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PATHOLOGY AND PATHOGENESIS OF THE DIFFUSE COLLAGEN DISEASES*

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PART I OF THREE PARTS

A LITTLE more than a decade ago the late Dr. G. Lyman Duff delivered a lecture to the Royal College of Physicians and Surgeons of Canada on the pathology of the diffuse collagen diseases.[19] Duff criticized the concept of "diffuse collagen diseases"[57] as system diseases and suggested that these maladies be regarded as *tissue diseases*. They have, indeed, in due course come to be regarded as such, and it is as tissue diseases that I intend to discuss them.

It is perhaps important to stress the fact that all elements of connective tissue are involved in the so-called collagen diseases and that "diseases of connective tissue" would be more appropriate than "collagen diseases". However, as Duff pointed out, "the term 'collagen diseases' seems to have come into current use not so much because of its strict propriety but as a matter of convenience and bre ity".

In discussing the collagen diseases I would like first to make a few statements about the morphology and chemistry of connective tissue as far as this is pertinent to our topic, then discuss briefly the pathology of the various diseases, and finally give an account of newer morphological and experimental data which shed some light on the nature of these maladies.

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The personal findings presented in Part I of this paper represent studies in progress, supported by a grant-in-aid from the Canadian Arthritis and Rheumatism Society; those in Parts II and III represent work carried out between 1953 and 1956 at Queen's University, Kingston, Ontario.

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MORPHOLOGY AND CHEMISTRY OF CONNECTIVE TISSUE

Connective tissue is composed of cellular and intercellular elements.

The *cellular elements* are derived from primitive (undifferentiated) mesenchymal cells. Of particular significance in the diseases under discussion are fibroblasts (Figs. 1 and 5), histiocytes and plasma cells (Figs. 2 and 6). The fibroblasts are instrumental in the formation of connective tissue; histiocytes function as phagocytes and are referred to as macrophages; plasma cells produce antibody. Mast cells produce heparin, but are also known to be very rich in histamine and serotonin. The last two substances play a role in vascular permeability, which is an important factor in the development of lesions in the collagen diseases. It has been postulated that the eosinophils act as inactivators of histamine and histamine-like substances. The function of the lymphocytes is obscure.[77] Ehrlich[21] suggested that they may function as trephocytes ("Nährmutterzellen" = nursing cells). Burnett[9, 10] hypothesized that lymphocytes carry a genocopy of the antigenic determinants which they transmit to the immunologically competent cells of the "mesenchymal clone".

The *intercellular elements* of connective tissue are either formed or amorphous. The formed elements comprise collagenic, reticular and elastic fibres, whereas the amorphous ones consist of ground and cement substances and of basement membrane. The ground substance fills in the spaces between the cells and forms intercellular elements. When it binds fibres together it is referred to as cement substance. Basement membrane forms boundaries, e.g. between glands and their supporting connective tissue.

Collagenic fibres (chemically, collagen) consist of very delicate unbranching fibrils which are held together by a small amount of cement substance. The term fibril in the past has been used in reference to the smallest units visible under the light microscope. Today the term is applied to the submicroscopic (electron microscopic) fibril.[122, 137, 142] (A further subdivision into "elementary fibrils" can be achieved only by treatment with acetic acid and heat.)[102] The fibrils have cross-striations, referred

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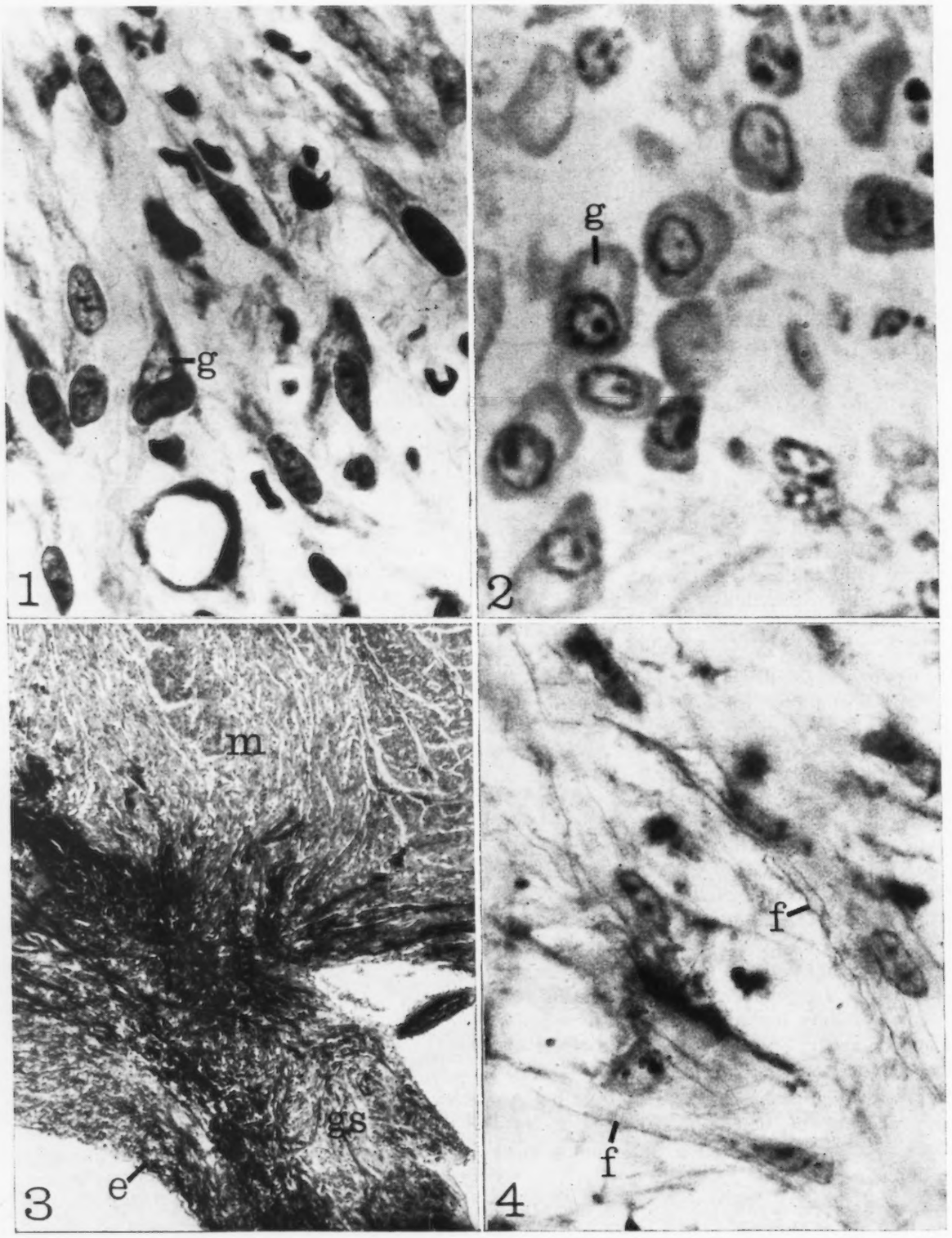


Fig. 1.—Proliferating fibroblasts in wound produced experimentally in a rabbit by incising the skin. Note the pronounced nucleoli, and the variations in density in the cytoplasm. The darkness or basophilia of the cytoplasm is due to the presence of ribonucleoprotein. The central pale area of the cytoplasm (g) corresponds to the Golgi apparatus. Compare with Fig. 5. Pentachrome I, × 660. **Fig. 2.**—Proliferating plasma cells in Arthus lesion of rabbit's skin. These cells are characterized by an eccentric nucleus, basophilic cytoplasm and a prominent so-called juxtanuclear halo (Golgi= g). Compare with Fig. 6. May—Grünwald-Giemsa, × 1610. **Fig. 3.**—Normal heart valve of middle-aged man. All extracellular elements of connective tissue are present. In the centre the black fibres (red in section) represent collagenic fibres. Elastic fibres and membranes (e) are seen best in the left lower corner (black in section) and ground substance (gs) is seen in the right lower corner (blue in section). Myocardium (m) is present in the upper half of the photograph (yellow in section). Compare with Fig. 8. Pentachrome II, × 55. **Fig. 4.**—This photograph shows Mallory's fibroglia fibres (f) which extend along the cytoplasmic borders of proliferating fibroblasts during the fibrillogenesis. Phosphotungstic acid hæmatoxylin, × 440.

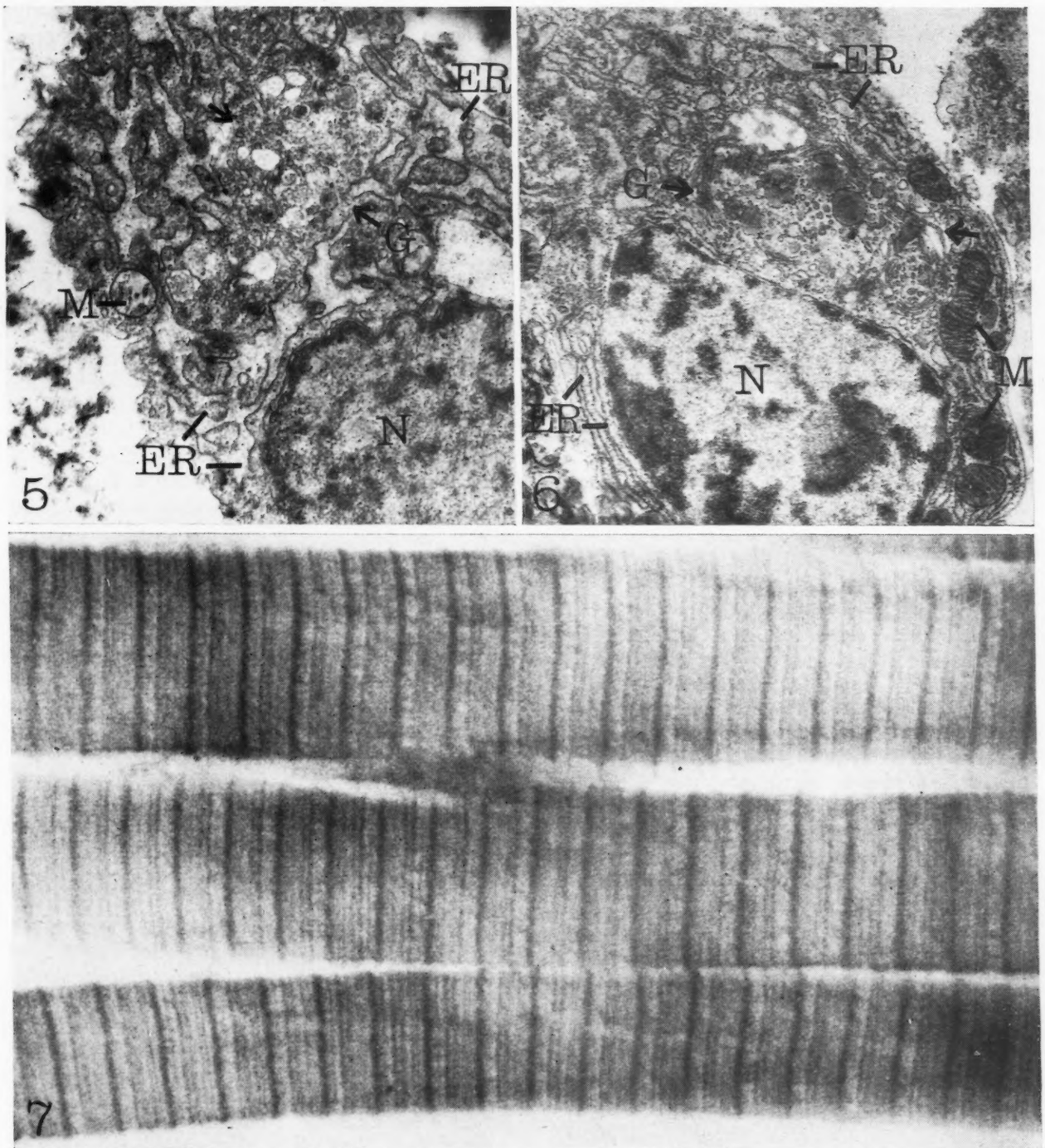


Fig. 5.—This electron micrograph shows part of a fibroblast, similar to those in Fig. 1. The basophilia seen in the light microscope is due to the presence of RNA granules, which coat the endoplasmic reticulum (ER) and fill the spaces between it. This is characteristic of cells which manufacture and secrete protein as in the case of the fibroblast precursors of the extracellular elements of connective tissue. Resting cells (fibrocytes) have little endoplasmic reticulum. Protargol stain, × 21,000. **Fig. 6.**—The plasma cell shown in this electron micrograph has a prominent Golgi apparatus (G), composed of vacuoles, microvesicles, lamellæ and globules. It corresponds to the juxtanuclear halo seen in the light microscope (Fig. 2). Similar to the fibroblast (Fig. 5), there is abundant endoplasmic reticulum (ER) in the cytoplasm. Note the prominent mitochondria (M). The nucleus (N) shows the characteristic condensation of chromatin. Protargol stain, × 18,500. **Fig. 7.**—This high-power electron micrograph shows three collagenic fibrils (microfibrils) from the Achilles' tendon of a rabbit. The tissue was fixed in osmic acid and the sections floated on phosphotungstic acid to demonstrate the periodicity and inter-period bands, × 176,000.

to as axial periodicity, with bands at regular intervals of approximately 640 A (Figs. 3, 7 and 9).

Reticular fibres (chemically, reticulin) form a network or reticulum and are found mainly in parenchymatous organs, such as the kidney or liver, and in lymphoid tissue, but are also found throughout the body. Of significance is the reticular framework of arteries, structures so often involved in the collagen diseases. Reticular fibres have a similar periodicity to collagenic fibres in the electron microscope, but while collagenic fibrils measure from 300-1600 A in width, reticular fibrils are only about 100 A wide. Reticular fibres contain an amorphous substance which is said to be responsible for certain characteristics (argyrophilia and intense staining with periodic acid Schiff

(PAS) reagent), not encountered in collagenic fibres.[112]

Chemically, collagen is characterized by an abundance of the amino-acids glycine, proline and hydroxyproline and a low concentration of sulphur-containing aromatic amino-acids.[44, 123] This knowledge was found of use in the study of the composition of fibrinoid, as will be pointed out later. Whereas the protein composition of collagen and reticulin is similar, reticulin contains bound fatty acids and has a greater concentration of carbohydrate.[35, 62, 141] Investigators in Montreal[36] cleared some of the controversies concerning the nature of the carbohydrate fraction of connective tissue fibres. They found two carbohydrate fractions in various connective tissues, including collagen from tendon and reticulin from lung. Fraction I was rich in glucuronic acid and represented acid mucopolysaccharide, whereas fraction II, which was rich in aldoses, represented a new, heretofore undescribed, component of connective tissue. Whereas acid mucopolysaccharides probably derive from the ground and cementing substance, fraction II, which is more abundant in reticulin than in collagen, is likely a component of the fibres.

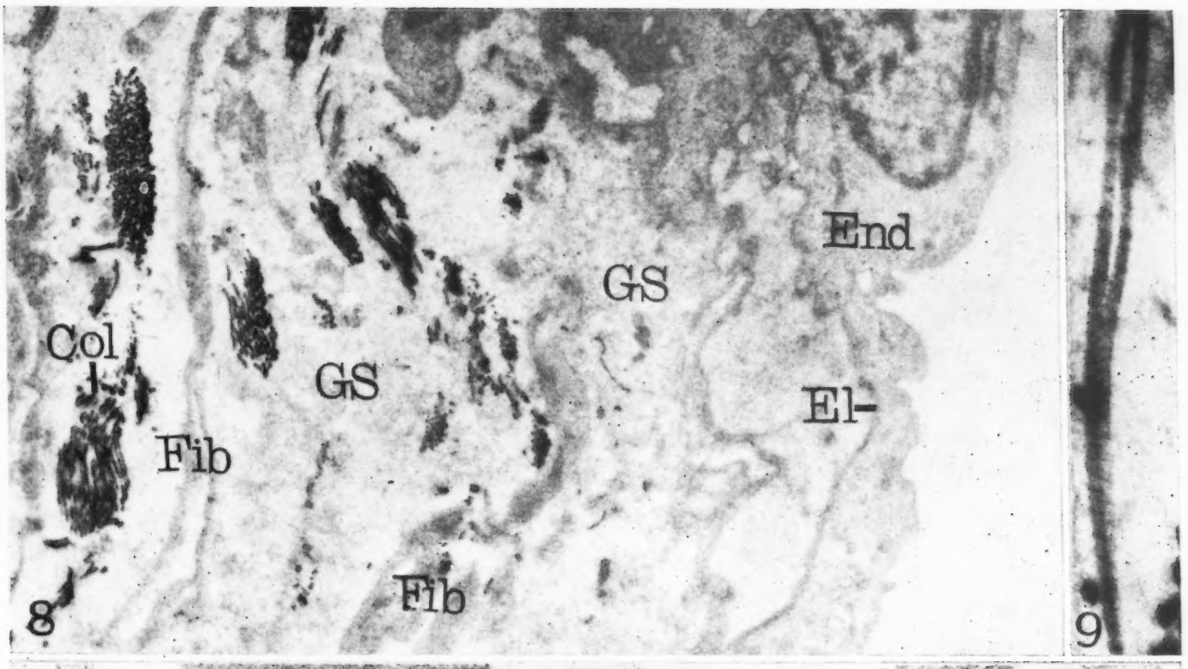
Elastic fibres (chemically, elastin) may form a network in loose connective tissue, they may form thick ligaments (e.g. the ligamentum flavum), or they may form fenestrated membranes, as in arteries (Figs. 3, 11). With the electron microscope no fibrils can be seen in an elastic fibre or membrane.[67] The protein of elastic tissue is referred to as elastin. It consists of two fibrous proteins (α and β). These have a similar composition with a high content of glycine, alanine, valine and proline, a low content of hydroxyproline and a very low content of polar residues.[66, 67, 123]

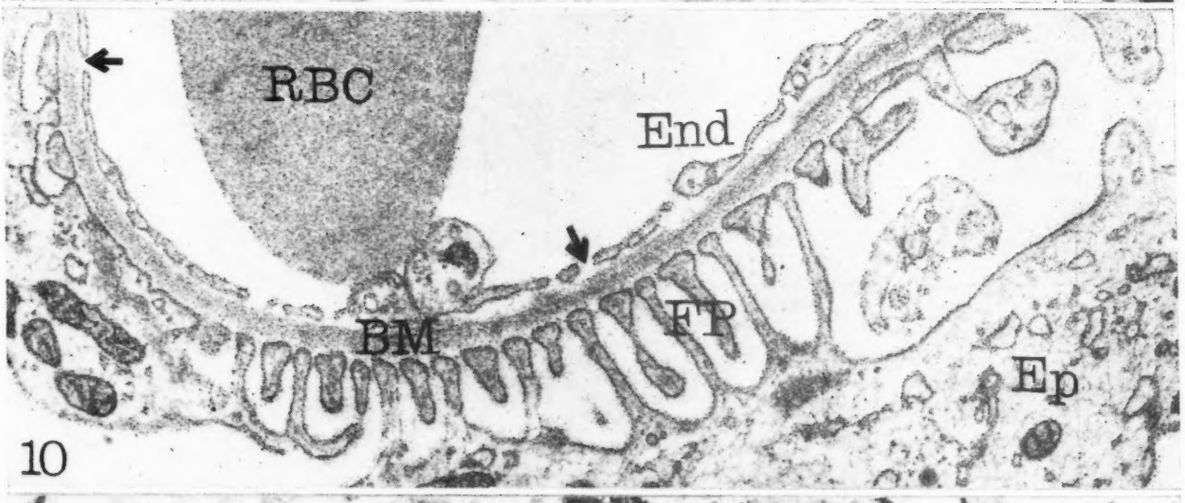
The *ground substance* of connective tissue is difficult to recognize unless specifically stained. It fills the space between the cellular and formed intercellular elements of connective tissue (Figs. 3 and 8). Whereas early investigators[65] thought that ground substance was lamellar, Bensley[8] described it as an amorphous substance of gelatinous consistency. The physical state of ground substance (gel or sol) is thought to depend on its degree of polymerization or depolymerization.[32] The significance of ground substance in the pathology of the collagen diseases lies in the fact that lesions develop mainly in connective tissue in which ground substance is very abundant, e.g. vessels, heart valves and joints. Whereas until recently[123] the protein component of ground substance has received little attention, the carbohydrate (i.e. acid mucopolysaccharide) has been thoroughly investigated by Meyer.[84, 85] Acid mucopolysaccharides have two components: hexosamine and hexuronic acid. They occur free (hyaluronic acid) or as esters of sulphuric acid (chondroitin sulphates). The esters are believed to be in loose combination with proteins of high molecular weight. Several types of acid mucopolysaccharide have been isolated (hyaluronic acid, chondroitin, chondroitin sulphates A, B and C, keratosulphate and heparin sulphate). These occur in various combinations in the various tissues. While collagen is digested by collagenase[44] and elastin by elastase,[3] acid mucopolysaccharides are hydrolyzed by hyaluronidases.[83] The susceptibility of mucopolysaccharides to enzymatic breakdown varies considerably. The proteins to which the mucopolysaccharides are bound have just begun to be studied.[123] The mucoprotein of cartilage matrix contains, in contrast to fibrous proteins, tyrosine. It also contains nitrogenous and non-nitrogenous components other than amino-acids. They are said to be important in the maintenance of connective tissue.

The nature of *basement membrane* is still controversial. Some of the early histologists regarded it as a condensation of reticular fibres. Others think that basement membrane is composed of a hyaline material, but supported by reticular fibres. There are no fibres within basement membrane when examined with the electron microscope (Fig. 10). Gersh and Catchpole[32] thought that basement membrane was a condensation of ground substance. However, it does not seem to have the same chemical composition as ground substance. Basement membrane stains intensely with the periodic-acid-Schiff stain, but faintly with acid mucopolysaccharide stains. It would appear that basement membrane contains fraction II, isolated by Glegg *et al.*,[36] but little, if any, of their fraction I. It is possible that some of the carbohydrates demonstrated in reticular fibres [36, 141] derive from basement membrane, with which these fibres are often intimately associated (e.g. in the kidney).

A few remarks seem pertinent to the *staining properties* of connective tissue. Whereas both collagenic and reticular fibres stain with aniline dyes, such as aniline blue or fast green in Masson's trichrome, only the reticular fibres are argyrophilic, i.e. impregnate with silver. Certain dyes (resorcin-fuchsin, orcein) stain elastic fibres specifically. The PAS (periodic-acid-Schiff) technique stains most components of connective tissue, but while some (collagenic fibres, ground substance) stain only moderately, others (reticular fibres, basement membrane) stain intensely. PAS-positivity is known to be due to the presence of carbohydrates (1,2 glycol groups) in the tissues. Acid mucopolysaccharides in the ground and cement substances can be demonstrated by metachromasia when stained with basic aniline dyes (e.g., toluidine blue), or better, with the new stain alcian blue[126, 135] and with Hale's colloidal iron.[45, 100] Complex staining methods have been developed which stain differentially the various components of connective tissue.[69, 91]

A knowledge of the *formation of connective tissue* is important for the understanding of sclerosis which occurs in the collagen diseases. Before describing newer work on this subject I wish to mention two observations which were made long





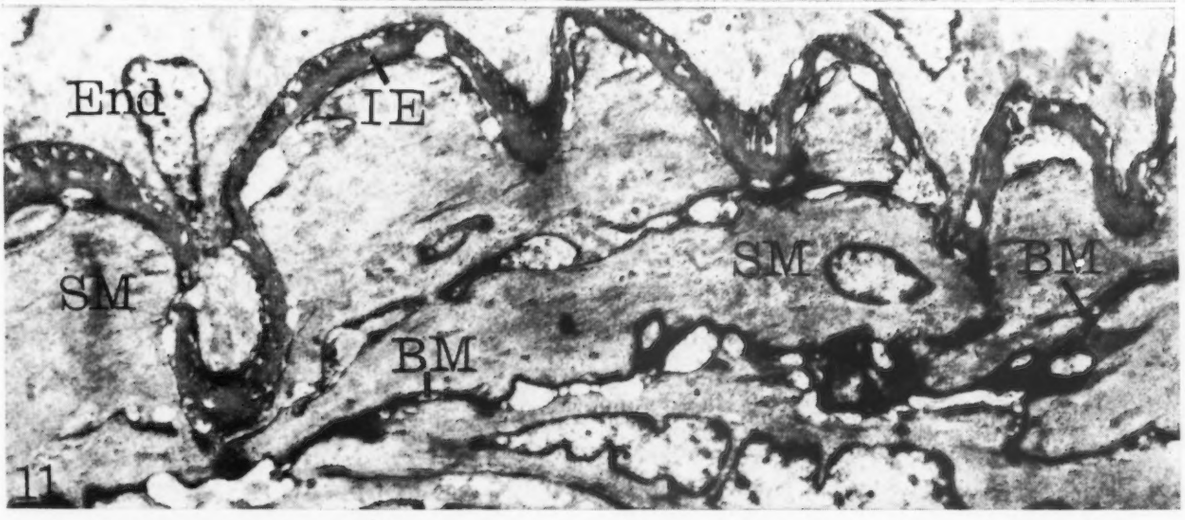
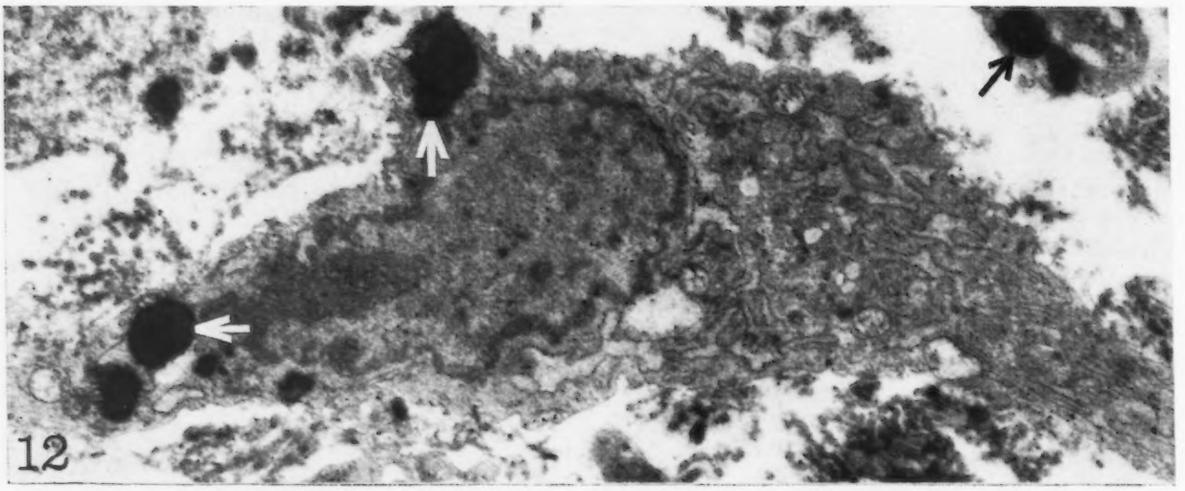


Fig. 8.—Mitral valve of rabbit. To the right there is the lining endothelium (end) sitting on the elastic membrane (El). Tapering processes of fibroblasts (Fib) are seen as dark grey elongated structures. Collagenic fibres (Col), composed of numerous fibrils, are seen in black. The grey homogeneous material between the fibres and cells is ground substance (GS). Compare with Fig. 3. Phosphotungstic acid stain, × 12,500. **Fig. 9.**—This electron micrograph shows one of the collagen fibres seen in Fig. 8 at a higher power. Note the characteristic periodicity of collagen. Phosphotungstic acid stain, × 55,000. **Fig. 10.**—Portion of capillary loop of glomerulus of a dog. The basement membrane (BM) consists of an electron dense (dark) middle layer (lamina densa) and two light outer layers (lamina rara interna and externa). The attenuated endothelium (End) abuts on to the lamina rara interna. The arrows point to fenestræ in the endothelium. The epithelium (Ep) inserts with foot processes (FP) into the lamina rara externa. Chromium chloride stain, × 24,600. **Fig. 11.**—The endothelium (End) and inner half of the media are shown in this branch of the renal artery of a dog. The internal elastic membrane (IE) is seen as a grey wavy band. It contains many fenestræ and is limited towards both endothelium and media by a delicate black line of basement membrane. Similar basement membrane material (BM) separates the smooth muscle cells (SM) of the media. It corresponds to structures stained red-purple by the periodic-acid-Schiff reagent in light microscopic sections. Periodic acid and silver methenamine stain, × 5500.



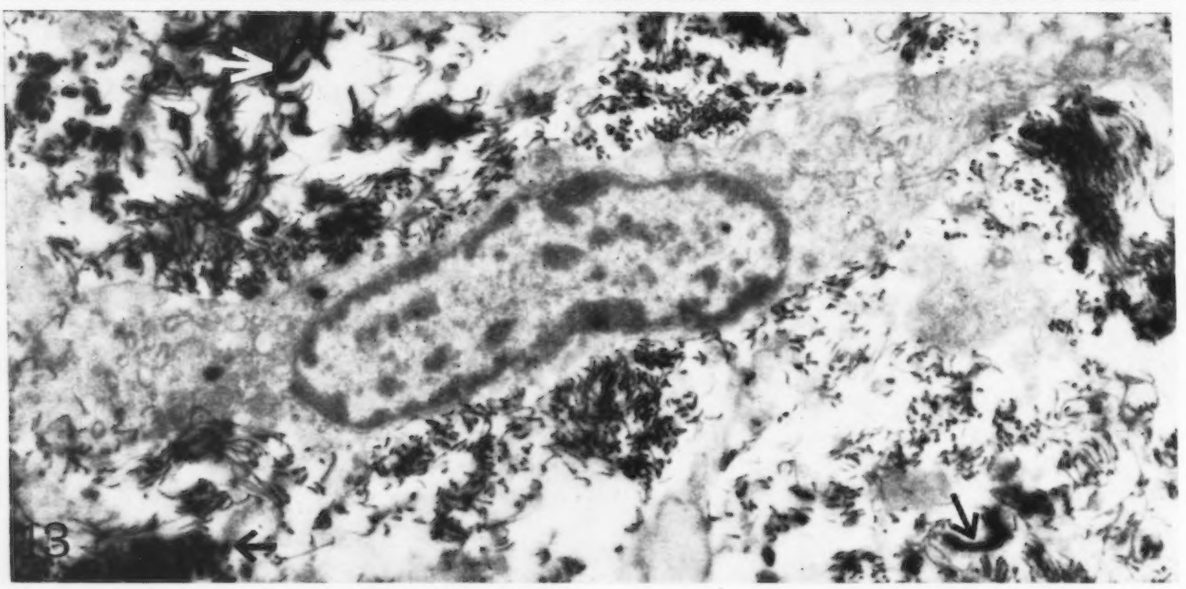


Fig. 12.—Proliferating fibroblast in 4-day-old skin wound of rabbit. The arrows point to black globules surrounded by a limiting membrane. These correspond to PAS-positive (mucoprotein) globules described by many in the light microscope. They probably represent products of the fibroblast and are comparable with Russell bodies of plasma cells. Protargol, × 12,000. **Fig. 13.**—This is a fibroblast from a 7-day-old skin wound. The arrows point to old (mature) collagen fibrils which were present in the dermis before the incision was made. All the delicate fibrils which are present around the cell are newly formed fibrils (so-called primary fibrils). Note that no fibrils are present within the cytoplasm of the cell. Phosphotungstic acid stain, × 10,000.

ago by histologists. One is that proliferating fibroblasts, as in granulation tissue, have a basophilic cytoplasm when examined in the light microscope (Fig. 1). The second is the observation of Mallory[72] that proliferating fibroblasts have so-called fibroglia fibres or tonofibrils in their cytoplasm (or at the border between cytoplasm and extracellular tissue) extending into the surrounding tissue (Fig. 4). Recent electron microscopic observations[52, 108, 109, 136-138] explain some of these phenomena and their relation to fibrillogenesis. Cells which manufacture and secrete protein are basophilic when examined with the light microscope, owing to high concentration of RNA in their cytoplasm. They are found to contain so-called rough-surfaced vesicles when examined by electron microscopy.[98] Such structures have indeed been found in the cytoplasm of fibroblasts (Fig. 5) which synthesize collagen or more likely its precursor.[52, 109] Mallory suggested that connective tissue fibres arise by differentiation of the cytoplasm of fibroblasts into fibroglia, which are later transformed into collagenic fibres. The nature of these fibroglia fibres has not been identified as yet. Porter and Pappas[109] believe that they may represent so-called "stress fibrils".

Wassermann[136, 137] found "primary fibrils" inside the cytoplasm, while "true" fibrils (with the characteristic periodicity) were found only intercellularly. Jackson[52] showed that the first fibrils which developed in tendons of chick embryos were within the cytoplasm of fibroblasts. The periodicity of these early fibrils was first 210 A, but later became that of mature collagen (640 A). In studies presently in progress[145] were found the primary fibrils developing in a wound always extracellularly, but abutting on the fibroblasts (Fig. 13). These findings are in agreement with those of Porter and Pappas.[109]

The presently accepted concept of fibrillogenesis is that ". . . the fibres are forming at the surface of the cell",[109] and that the fibroblast forms ". . . building blocks, which aggregate outside the

cell".[137] Thus the immediate products of the fibroblast are smaller units than fibrils. In the ground substance these small units or building blocks aggregate to form fibrils. It is generally accepted that the maturing fibril incorporates polysaccharides, predominantly chondroitin sulphate. The latter gives collagen its stability.[53]

For the understanding of the sclerosis which occurs in the collagen diseases it is important to mention that in tissue cultures collagen fibres develop from plasma proteins in the absence of cells. However, metabolic products of cells, "fibroblastic juice" (presumably enzymes), are necessary for this type of fibrillogenesis. These studies[17] were carried out in the laboratory of Rössle,[117, 120] who introduced the concept of "acellullar organ sclerosis", which is likely a common process in the collagen diseases. The nature of this, presumably abnormal, connective tissue is presently being investigated in our laboratory.

In contrast to collagenic fibres, little is known about the formation of elastic fibres.[137] Formation of ground substance has been studied by several investigators. Whereas some workers[1] believe that mucopolysaccharides of the ground substance are secreted by mast cells, the majority[32, 42, 70] agree that they are formed by fibroblasts. Gersh and Catchpole[32] and Jackson[52] observed PAS-positive (mucoprotein-containing) granules in proliferating fibroblasts. These probably correspond to dense globules seen in electron micrographs in fibroblasts in the early phase of wound healing (Fig. 12) and may be related to ground substance synthesis.

General Pathology of Connective Tissue

As Duff[19] pointed out in referring to the intercellular structures of connective tissue, "all of the alleged functions of the fibrous connective tissue . . . are purely passive". Among the components of connective tissue only the cells are living structures, says Duff. "The intercellular fibres and the ground substance are quite inert. They are formed by or under the influence of the fibroblasts, but they are themselves incapable of active response and can only be acted upon by alterations in their immediate environment". Therefore, it does not seem to be appropriate to speak of "necrosis" in connection with collagen or ground substance. However, in referring to changes like those in the centre of rheumatoid nodules, "necrosis" is being used for want of a better term.

Of the various changes encountered in the extracellular elements of connective tissue in the collagen diseases may be mentioned fibrinoid deposition, mucinous œdema, hyaline formation and sclerosis. These will be discussed in more detail in the third part of this paper which deals with recent developments in the pathology of the collagen diseases. Cellular changes are characterized by proliferation of mononuclear cells (macrophages, lymphocytes and plasma cells). With some exceptions polymorphonuclear infiltration is scanty.

The acute lesion in the diffuse collagen diseases is an *allergic inflammation*. The concept of allergic or allergic-hyperergic inflammation was coined by Rössle.[114-116, 118, 119] He defined allergic inflammation as quantitatively but not qualitatively different from normergic (ordinary) inflammation. It is characterized by rapid development and by massive exudation of protein-rich fluid. Klinge's[60] studies on rheumatic diseases and their experimental counterpart were based on Rössle's concept of allergic inflammation. Later, Klemperer *et al.*[57, 58] coined the concept of "collagen diseases", but denied the allergic pathogenesis in some of them. Today the pendulum has swung back to hypersensitivity (as will be described in more detail in the third part of this paper).

END OF PART ONE

PHENETHICILLIN

It appears that the major claims for the superiority of phenethicillin (Broxil) (Syncillin) over penicillin V are not well founded. More data are needed to permit a complete comparison of these and other penicillins, particularly in their effects on infections caused by penicillinase-produced staphylococci, but it is fair to say that the new, so-called synthetic penicillin possesses no demonstrated virtues of importance that should impel one to choose it over other available forms. This conclusion was also reached in an annotation that appeared in the *British Medical Journal* shortly after the availability of the new penicillin was announced in the public press in England and also subsequently, in an editorial that appeared in the *New York State Journal of Medicine*. In each instance the writer hailed the advent of the new semisynthetic penicillin more for its portent of possible things to come than for any intrinsic value in the product that was actually made available.—Editorial: *New England J. Med.*, 263: 361, 1960.

JENNER AND VACCINATION

Edward Jenner's great contribution of vaccination against smallpox stands out perhaps unequalled in the domain of public health and preventive medicine. But both Jenner's work and Jenner's personality were variously judged at the time. It was claimed that vaccination was based on unsound grounds and that Jenner himself was little more than a quack. The idea that an attack of cowpox safeguarded the victim against smallpox was said to be prevalent among the dairy hands in Gloucestershire, and Jenner was a Gloucestershire boy. In 1796 Jenner inoculated the skin of a lad, James Phipps, with material from a cowpox vesicle on the hand of a dairymaid, Sarah Nelmes. The vaccination took, and later inoculation of smallpox material failed to produce disease. Jenner sent a report of this observation to the Royal Society, but it was not accepted, and finally Jenner was driven to publish his experiences himself.—Bloomfield, A. L.: Some Footnotes to Medical History, *A.M.A. Arch. Int. Med.*, 106: 293, 1960.

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GUANETHIDINE* ADMINISTRATION IN 28 HYPERTENSIVE PATIENTS†

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IN THEIR endless search for an ideal antihypertensive agent, research workers often find a most promising new drug in a fortuitous way. It was in such a manner that Maxwell *et al.*[1] in their pharmacological studies of methylphenidate§ demonstrated that this central nervous stimulant possessed very interesting cardiovascular properties (Table I) of guanethidine. Its structure differs from that of SU-4029 in that it possesses an 8-membered instead of 7-membered ring and a terminal guanidyl instead of an amidoxine group. Pharmacological studies of this compound in dogs revealed also a prolonged action and more marked antihypertensive effects (Table I) than those obtained with twice the dosage of SU-4029. According to Maxwell *et al.*[5] guanethidine would chronically interfere with the release and/or the normal distribution of the neurohumoral transmitter at the sympathetic neuromuscular junction.

This presentation will deal briefly with the clinical investigation of peroral administration of SU-4029. The clinical evaluation of peroral and parenteral administration of guanethidine will be reported more extensively.

TABLE I.—COMPARISON OF PARENTERAL ACTION OF THREE COMPOUNDS ON BLOOD PRESSURE OF DOGS

	Methylphenidate[1]	SU–4029[2]	SU–5864 = guanethidine[5]
		30 mg./kg. body weight one single intravenous injection	15 mg./kg. body weight in two intravenous injections 15 minutes apart
	Short duration of action	Prolonged (2–6 weeks) duration of action	Prolonged (4 days to 3 weeks) duration of action
(A) On normal blood pressure		Not notably affected	Slightly hypotensive
(B) On amphetamine and ephedrine-induced hypertension	Eliminated	Markedly antagonized	Markedly antagonized
(C) On hypertension produced by the carotid occlusion reflex	Antagonized	Markedly antagonized (up to 3 weeks)	Markedly antagonized (up to 6-7 days)
(D) On neurogenic hypertension		Moderately lowered	Profoundly lowered
(E) On renal hypertension	Moderately lowered	Markedly lowered	Profoundly lowered

antagonizing carotid occlusion pressure responses, blocking the hypertensive effects of amphetamine and ephedrine, and lowering the arterial pressure of dogs with renal hypertension. In connection with these studies, hexahydro-1-azepinepropionamidoxine dihydrochloride (Ciba SU-4029) was then prepared (see Fig. 1). Maxwell *et al.*[2] were able to show in dogs (Table I) that this compound, although chemically different from methylphenidate and not a motor stimulant, had marked antihypertensive effects and prolonged action. Other data suggested that its principal site of action might be the smooth muscle of vessels.[3]

A distant chemical relative was then synthesized by the same group,[4] (2(octahydro-1-azocinyl)-ethyl)-guanidine sulfate (SU-5864) (see Fig. 1). This compound has been given the generic name

PATIENTS AND METHODS

In each hospital patient, recumbent and upright blood pressure readings were taken at hourly intervals from 8 a.m. to 8 p.m. during control and therapeutic periods. For patients seen at weekly intervals at the Hypertension Clinic of the Hôtel-

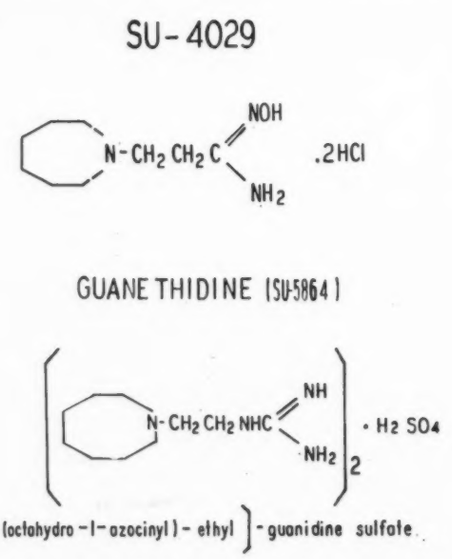

Fig. 1.—Chemical structures of the two compounds studied, SU-4029 and guanethidine (SU-5864).

*Guanethidine (Ismelin) and SU-4029 have been generously supplied by Dr. Walter Murphy, Ciba Company Limited, Montreal.

†From the Clinical Research Department, Hôtel-Dieu Hospital, Montreal. This report was presented in parts by Jacques Genest at (1) the meeting of the Canadian Federation for Clinical Investigation, Montreal, January 1960; (2) a Symposium on Hypertension, in Memphis, Tennessee, April 1960.

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‡Postgraduate Medical Research Fellow of the National Research Council, Ottawa.

§Methylphenidate (Ritalin), Ciba Company Limited, Montreal.

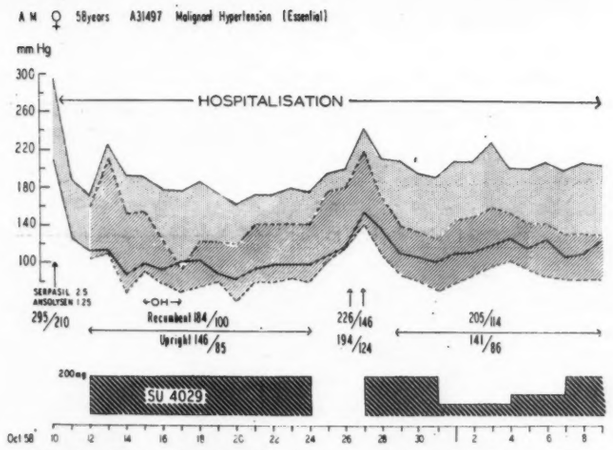

Fig. 2.—This 58-year-old woman with malignant hypertension was admitted in hypertensive crisis which necessitated parenteral administration of reserpine 2.5 mg. (Serpasil) and of pentolinium 1.25 mg. (Ansolysen). The effect of SU-4029 on blood pressure in recumbent and upright positions is quite striking.

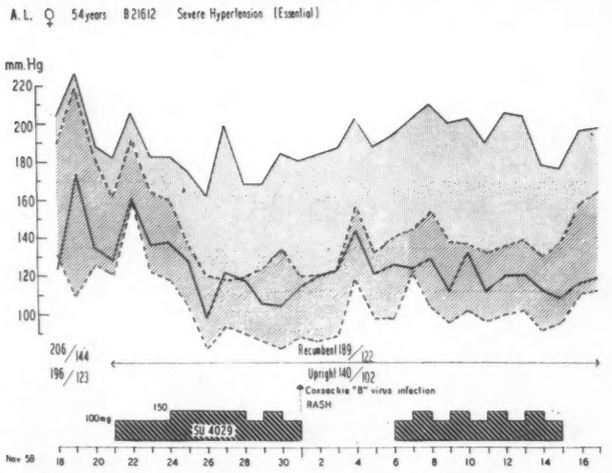

Fig. 3.—This 54-year-old patient with severe essential hypertension had a marked lowering of her blood pressure in the upright position during oral administration of SU-4029. She developed a skin rash and laboratory evidence of Coxsackie virus infection.

Dieu Hospital, recumbent and upright blood pressure readings are represented by means of three readings taken in each position.

The clinical investigation of SU-4029 consisted of peroral administration of 100 to 300 mg./day to four patients (three women and one man) with essential hypertension (one malignant, one severe and two benign) aged 16 to 58 years. Average period of administration was 8 days, ranging from 2.5 to 13 days.

Guanethidine (SU-5864) was administered on a long-term basis to 28 patients, 13 men and 15 women. Average age was 48, ranging from 22 to 69. Of these 28 patients, 19 had essential, 4 renal and 5 malignant hypertension. The average period of administration was 14 weeks (range of 5 to 24 weeks). Average effective dose was 50 mg. per day, usually given either in a single dose after breakfast or in two divided doses after breakfast and supper.

In addition, the drug was studied after acute intravenous injection for its effect in hypertensive patients and in a patient with phæochromocytoma.

RESULTS

(A) *SU-4029*

Recumbent blood pressure was significantly decreased and orthostatic hypotension was seen with varying frequency in all four patients. The hypotensive effect of SU-4029 in a patient with malignant hypertension admitted to hospital in hypertensive crisis is quite striking (Fig. 2). Peroral administration of SU-4029 kept the blood pressure to normal levels in upright position with a short period of orthostatic hypotension. Cessation of the drug rapidly returned the blood pressure to hypertensive levels, and re-administration of SU-4029 caused a rapid fall of blood pressure to normal levels in upright position.

Side effects.—Use of this compound was short-lived because of its toxicity. This is well illustrated in two of our patients. After ten days' administration in the first patient (Fig. 3), a woman 54 years of age with severe essential hypertension, it was necessary to stop the drug on account of slight cervical and axillary lymph node enlargement, enanthema and a diffuse skin rash of four days' duration, especially on the limbs. Washings from the patient's throat, when injected into newborn mice, caused lesions identical to those produced by Coxsackie B virus. Neutralization tests showed an 8-fold increase in antibodies for the Coxsackie B 1 virus. In the other patient (Fig. 4), a 16-year-old boy with benign essential hypertension, severe orthostatic hypotension occurred after three days' administration of 300 mg./day. The drug had to be stopped and was resumed the next day. After three days' administration of 200 mg./day, the patient developed slight fever (99.2° F.), cervical lymph node enlargement, conjunctivitis, rhinitis, enanthema and a diffuse morbilliform skin rash, which disappeared four days later. Urine, stools and

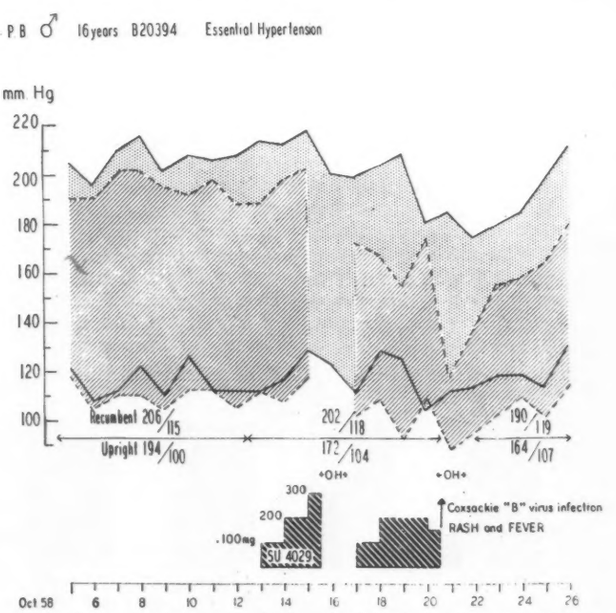

Fig. 4.—Administration of SU-4029 had to be stopped after two and one-half days because of severe orthostatic hypotension. Readministration of the drug was followed by slight fever, skin rash and evidence of Coxsackie virus infection.

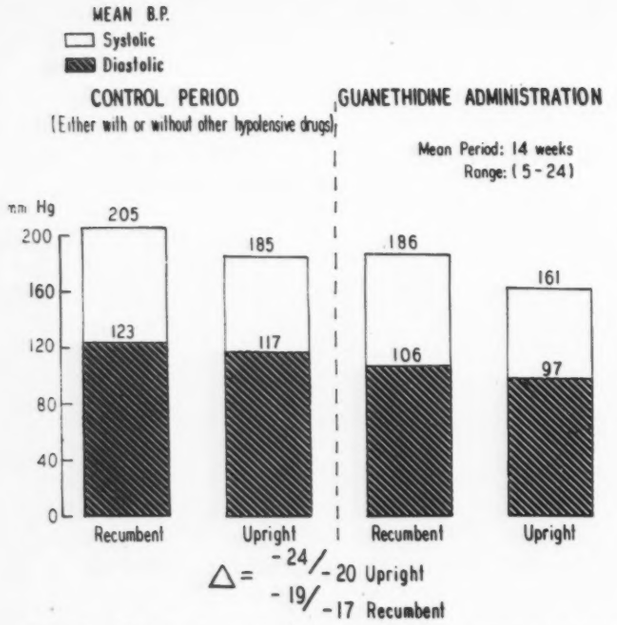

Fig. 5.—Effect of guanethidine on blood pressure of 28 hypertensive patients.

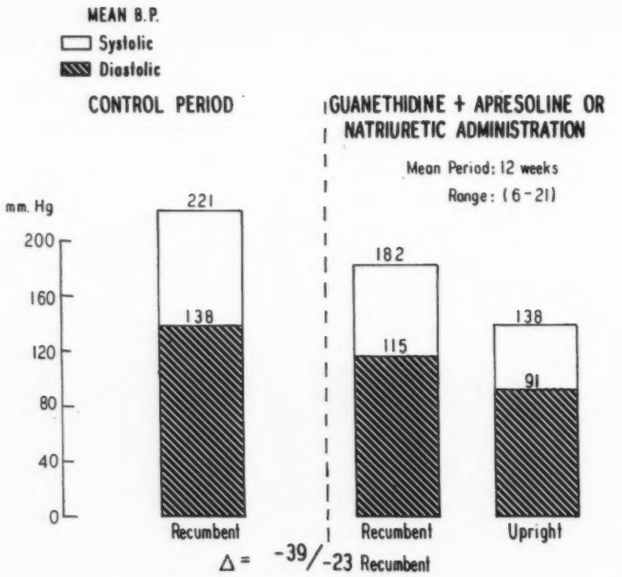

Fig. 7.—Effect of guanethidine combined with other hypotensive drugs on blood pressure of three hypertensive patients. The average blood pressures in recumbent position only are indicated for the control period. An insufficient number of readings in upright position was taken in two of the three patients and, therefore, the blood pressure in upright position is not indicated.

throat washings, when injected into newborn mice, produced lesions typical of those due to Coxsackie virus. This evidence was also supported by a marked rise in antibodies for Coxsackie B 4 and A 9 viruses in the neutralization tests.

This investigation was not continued further, and efforts were directed to the study of the new guanidine derivative, SU-5864.

(B) *Guanethidine (SU-5864)*

Peroral administration.—The overall effect of orally administered guanethidine in the 28 patients with arterial hypertension is shown in Fig. 5. The control period consisted either of blood pressure readings during at least four weekly visits to our clinic before administration of the drug, which was given alone or with other hypotensive agents, or of 24 hourly readings taken during the first 48 hours of hospital admission. There was an overall significant decrease in blood pressure of 24/20 mm. Hg in the upright position and of 19/17 mm. Hg in the recumbent position.

These 28 patients were further divided into three groups depending on the control period or on the period of administration of guanethidine either alone or combined with other drugs. Group A consisted of 13 severe hypertensive patients already receiving hypotensive drugs, including ganglionic-blocking agents, either mecamylamine or pempidine, for purposes of comparing hypotensive activity, side effects, and well-being of the patient, with the effects of guanethidine. In this group, replacement of the hypotensive drugs by guanethidine was accompanied by a further decrease in blood pressure of 16/10 mm. Hg in upright position and of 13/12 mm. Hg in recumbent position. Side effects were less frequent, less annoying and better tolerated when the patients were receiving guanethidine.

Group B consisted of 12 hypertensive patients who had control periods during which no hypotensive drug was given. In this group, guanethidine was administered alone for an average period of 14 weeks, ranging from 6 to 24 weeks (Fig. 6). The decrease in both systolic and diastolic pressures was 28/28 mm. Hg in upright position and 22/21 mm. Hg in recumbent position.

Group C consisted of three patients who had a control period during which no hypotensive drug was given. Guanethidine was administered in association with other hypotensive agents, a natriuretic drug and/or hydralazine (Fig. 7). The period of administration of the combined hypo-

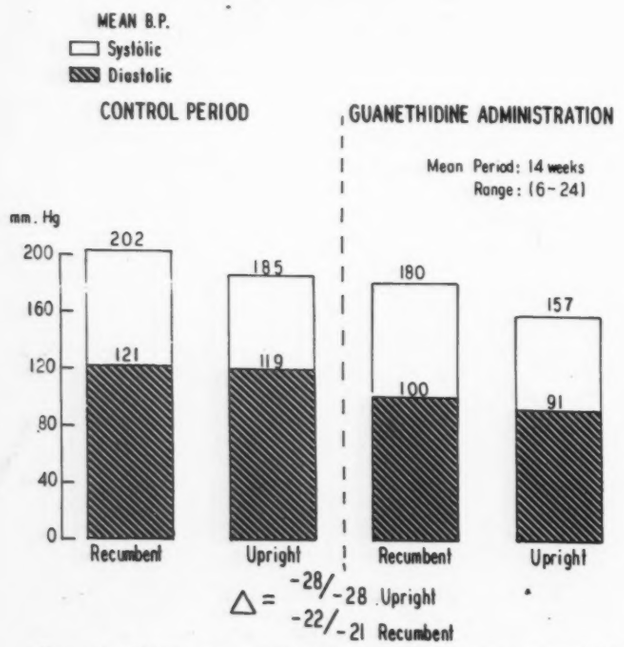

Fig. 6.—Effect of guanethidine on blood pressure of 12 hypertensive patients.

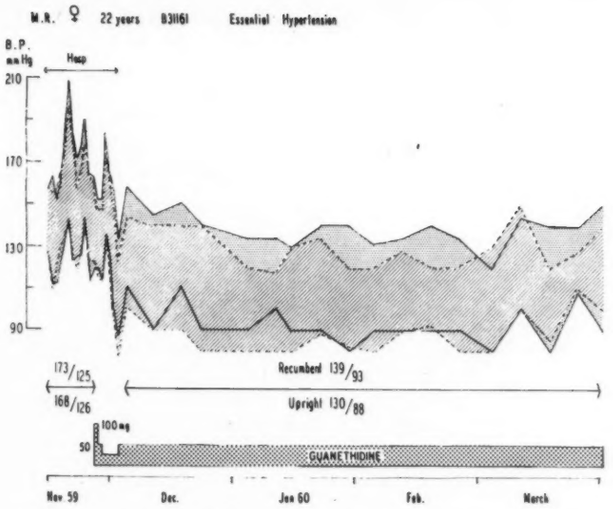

Fig. 8.—Administration of 50 mg. of guanethidine for a period of over four months brought the blood pressure down to normal levels in this 22-year-old woman with essential hypertension.

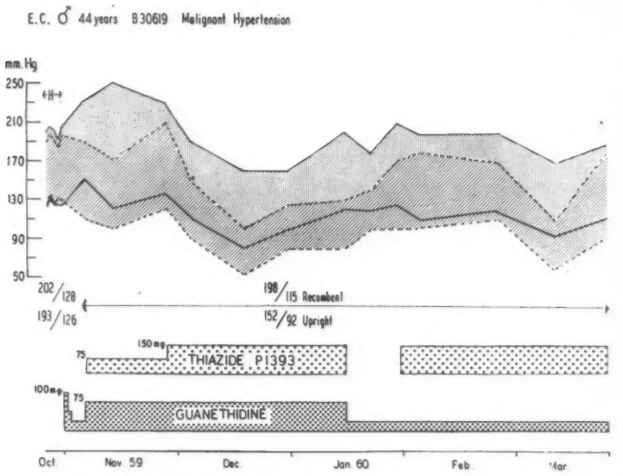

Fig. 9.—Hypotensive effect of a combination of guanethidine and a natriuretic drug of the thiazide series, P-1393.

tensive agents was 12 weeks, ranging from 6 to 21 weeks. The fall in recumbent blood pressure was 39/23 mm. Hg, and the average blood pressure in upright position in these three patients was brought to normal levels.

The hypotensive effect of guanethidine in two patients, one with malignant and one with essential hypertension, is illustrated in Figs. 8 and 9. Administration of 50 mg. per day of guanethidine for four months reduced the blood pressure of a patient with essential hypertension from control levels of 173/125 mm. Hg in recumbent position and 168/126 mm. Hg in upright position to normotensive levels in both positions (Fig. 8).

The combined effects of a thiazide derivative P-1393* and guanethidine in a patient with malignant hypertension are shown in Fig. 9. Blood pressure during control period was 202/128 mm. Hg in recumbent position and 193/126 mm. Hg in upright position. Simultaneous administration of guanethidine and a thiazide derivative P-1393 brought the blood pressure down to almost normotensive levels in upright position during the four and one-half months of combined administration.

Side effects.—Side effects encountered during administration of guanethidine in the 28 patients studied are described in Table II. Diarrhœa occurred in 15 out of 28 patients and could be easily controlled by simultaneous administration of belladonna or a synthetic anticholinergic agent. Orthostatic hypotension, defined as inability to remain in upright position, was encountered in 11 patients; excessive fatigue in 9; a pulse rate below 60 per minute in 3; inhibition of ejaculation in 3, priapism in 1. During prolonged administration, 4 patients (3 females and 1 male) with severe essential hypertension, developed, after periods varying from 10 to 22 weeks, acute peptic ulcer with melæna. These patients were receiving a mean dose of 37.5 mg. of guanethidine/day, given alone in two, in association with chlorthalidone* in a third, and with hydrochlorothiazide and hydralazine in the fourth. Roentgen films showed an ulcer on the lesser curvature in two, a duodenal ulcer in one, and a duodenal and gastric ulcer in the other. Before guanethidine therapy, a typical history of peptic ulcer was present in all, with bouts of hæmatemesis and melæna in one, and melæna in another, whereas roentgenography of the upper gastro-intestinal tract before drug administration revealed a very small ulcer of the duodenum in two and was negative in another.

TABLE II.—SIDE EFFECTS OF PERORAL ADMINISTRATION OF GUANETHIDINE IN 28 PATIENTS

Diarrhœa	15
Orthostatic hypotension	11
Excessive fatigue in the morning	9
Acute peptic ulcer	4
Bradycardia 60/min	3
Inhibition of ejaculation	3
Prolonged erection	1

*P-1393, Pfizer.

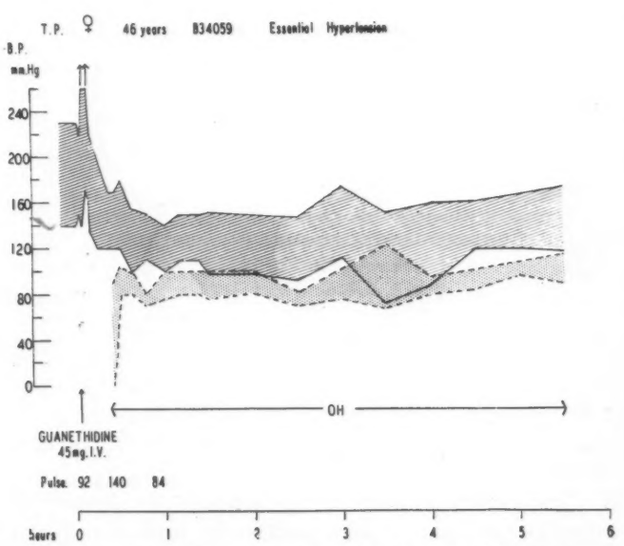

Fig. 10.—This figure illustrates the danger of intravenous administration of guanethidine in patients with essential hypertension. The sudden rise in systolic and diastolic pressures may produce life-threatening complications in patients with vascular lesions or with left ventricular failure.

*Hygroton, Geigy.

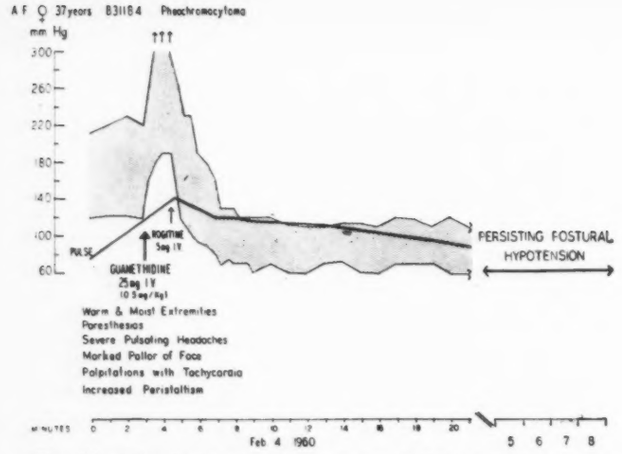

Fig. 11.—Illustration of the dangers of giving guanethidine by the intravenous route in a patient having, or suspected of having, a phæochromocytoma.

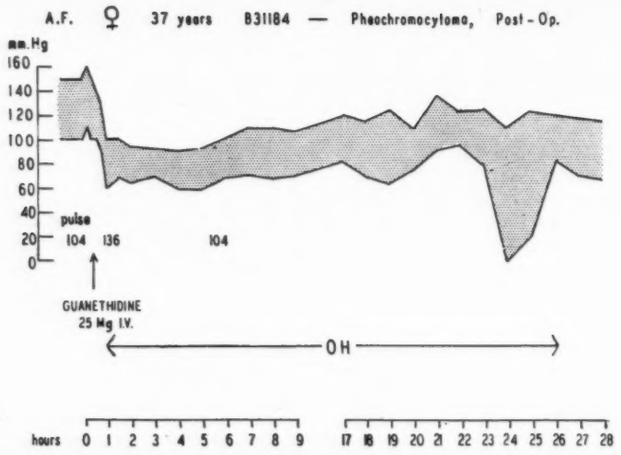

Fig. 12.—Administration of the same dose of guanethidine intravenously after removal of a phæochromocytoma in the same patient (Fig. 11).

Intravenous administration.—The intravenous effect of guanethidine at a dosage of 0.5 mg. per kg. body weight was studied in several patients with various types of hypertension. Fig. 10 shows the effects of intravenous administration of 45 mg. of guanethidine in a patient with essential hypertension. There was a short rise in blood pressure, with systolic pressure rising above 260 mm. Hg and diastolic to 175 mm. Hg. This lasted only for 90 seconds and the blood pressure fell rapidly to almost normal levels in recumbent position with concomitant orthostatic hypotension. Pulse rate increased also to 140 per minute, immediately after administration of guanethidine.

Guanethidine was given intravenously (Fig. 11), at a dosage of 0.5 mg. per kg. body weight, to a 37-year-old woman with a typical clinical history of phæochromocytoma, confirmed by pharmacological tests, chemical and biological studies of urinary catecholamines, and verified at operation. Because of previous information that guanethidine potentiated the hypertensive effect of noradrenaline in dogs, guanethidine was injected through a three-way stopcock, the side arm of which was already connected to a syringe containing 5 mg. of phentolamine.* The blood pressure for the 90 to 100 seconds after intravenous injection of guanethidine rose to levels above 300 mm. Hg systolic and 190 mm. Hg diastolic. During this short time, the patient's extremities became warm and moist, her face was very pale, and her pulse rate increased to 140 per minute. She complained of paræsthesiæ, severe pulsating headaches, palpitations and colicky pains in the abdomen. Immediate injection of 5 mg. of phentolamine brought about a very rapid and dramatic fall in blood pressure to normal levels, with postural hypotension persisting for the next four days.

The experiment was repeated in the same patient several days postoperatively, and the effects are illustrated in Fig. 12. The same increase in pulse rate was observed but there was no dangerous drop in blood pressure. Recumbent blood pressure decreased markedly for several hours, with concomitant orthostatic hypotension.

*Rogitine, Ciba.

COMMENTS

Page and Dustan[6] had already reported fever of unknown origin in two patients during successful peroral administration of SU-4029. Our clinical observation of two cases of fever, enanthema and diffuse skin rash with evidence of Coxsackie virus infection may either be interpreted as a simple coincidence on administration of the drug, or may indicate an enhancement of the susceptibility of these patients to Coxsackie virus infection.

Watery stools, passed two to eight times daily, and often preceded by borborygmi, abdominal cramps and an urgent need for defæcation, were present in 15 of our patients receiving peroral guanethidine. By simply dividing the dose of the drug in two, one-half after breakfast, the other after supper, it was sometimes possible to prevent or decrease the diarrhœa caused by the sympatholytic activity of the agent. In refractory cases, the addition of belladonna or a synthetic anticholinergic agent provided satisfactory symptomatic relief.

Careful observation of patients before or during peroral guanethidine therapy would be worth while for early detection of aggravation of peptic ulcer, especially in those who have a previous history of ulcer. Toxicity experiments in dogs showed no lesion of the stomach.[5] As noted by Richardson and Wyso,[7] oral guanethidine administration has a slow onset (24-48 hours) and a long duration of action which persists a few days after cessation of therapy. We have not yet observed any tolerance to the antihypertensive effects of the drug.

When guanethidine is given intravenously, the potential danger of provoking marked acute hypertension makes its use in patients with possible phæochromocytoma, or even with essential hypertension, quite dangerous. We feel that there is little need for its intravenous use in hypertensive patients, especially in those with evidence of vascular disease or left ventricular failure.

Recent data[8] in rats and rabbits suggest that lowering of blood pressure is obtained by chemical sympathectomy through depletion of noradrenaline from peripheral nerve endings.

SUMMARY

Guanethidine is a potent and well-tolerated sympatholytic drug which has a marked and prolonged hypotensive effect on patients with various types of arterial hypertension. The average effective dose is 37.5 to 50 mg./day. The drug may act by depletion of noradrenaline from peripheral nerve endings. It is slightly more effective with the patient in the upright than in the recumbent position.

Orthostatic hypotension and excessive fatigue, which are frequently observed, may be partially prevented by decreasing the dosage of guanethidine and by adding other hypotensive agents such as one of the natriuretic drugs and/or hydralazine. Diarrhœa is usually controlled by administering an anticholinergic agent or by dividing the daily dose. Combination of other hypotensive drugs with guanethidine is more effective in the treatment of patients with severe hypertension. Guanethidine must be used with caution in patients who have a past history of peptic ulcer, and its intravenous use is not recommended.

We are grateful to Dr. V. Pavilanis, Director, Virology Section, Institut de Microbiologie et d'Hygiène, University of Montreal, for the virological studies, and to Dr. R. Cleroux for permission to study the case of phæochromocytoma. We acknowledge the collaboration of Misses F. Salvail, R.N., R. Dansereau, R.N., P. Bourque, R.N., and Réjane Roy, R.N.

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LES RACHITISMES VITAMINO-RESISTANTS DE L'ENFANT*

P. ROYER,† *Paris, France*

TOUT RACHITISME non prévenu par l'administration régulière, précoce et prolongée de 500 à 1000 unités par jour de vitamine D et non guéri par une dose totale de 5 à 15 mg. de vitamine D, est dit rachitisme vitamino-résistant (R.V.R.).[17]

A. *Rachitisme vitamino-résistant d'origine digestive*

Fistules biliaires, ictères chroniques à selles décolorées, résections étendues du grêle et surtout maladies cœliaques et mucoviscidoses ont cette réputation ancienne de réaliser un R.V.R. par trouble de l'absorption intestinale de la vitamine D et du calcium.

En verité nous avons été surpris de la rareté des ostéopathies dans les fistules biliaires, les syndromes cœliaques et surtout les mucoviscidoses que nous avons examinées. Quand il existait des anomalies radiologiques du squelette, elles s'apparentaient plus à l'ostéoporose de la malnutrition protéique qu'au rachitisme ou à l'ostéomalacie. Lorsque le rachitisme était une certitude clinique, radiologique, biochimique, il a réagi habituellement, mais non toujours, à l'administration *parentérale* de 5 à 10 mg. de vitamine D. Dans une observation de syndrome cœliaque par intolérance à la gliadine, le régime sans gluten, sans adjonction de vitamine D, a permis la guérison du rachitisme en quelques semaines.

Par ailleurs, le problème du "rachitisme hépatique" survenant en dehors de tout ictère chronique n'est pas résolu. Friis-Hansen[9] est revenu sur cette question en 1956. Il conclut au rôle rachitigène de l'absence d'un facteur hépatique influençant la calcification ou prévenant la déminéralisation de l'os. Il y a là beaucoup d'hypothèse. Des cas anciens de "rachitisme hépatique", il convient de distraire: (a) ceux qui s'accompagnent d'un ictère comme celui de Friis-Hansen lui-même; (b) ceux qui correspondent à la juxtaposition d'une ostéopathie et d'une affection hépatique, toutes deux secondaires à une maladie du métabolisme comme dans la cystinose ou la dégénérescence hépatolenticulaire; (c) les cas familiaux, décrits par Dent et par Baber, de syndrome de de Toni-Debré-Fanconi, compliqué de cirrhose hépatique avec tyrosinurie dont le mécanisme reste obscur.

B. *Rachitisme vitamino-résistant d'origine rénale*

La dissociation du "rachitisme rénal", bien qu'encore inachevée, a conduit dans ces dernières années à des précisions intéressantes. A son propos, il nous faut progresser du plus simple au plus complexe.

(1) RACHITISME PAR INSUFFISANCE TUBULAIRE

(a) *Le "rachitisme rénal" hypercalciurique par acidose tubulaire*

Cette affection, décrite par Albright en 1940[1] chez un adolescent, a été retrouvée chez l'enfant comme chez l'adulte. Elle réalise un type très pur de rachitisme par "hypercalciurie".

*Conférence prononcée en novembre 1959 au Montreal Children's Hospital.

†Professeur agrégé à la Faculté de Médecine de Paris.

Son début est souvent tardif, et sauf dans l'observation de Schreiner, la maladie n'est pas familiale. On connaît ses signes: (a) arrêt de croissance; (b) soif vive et polyurie; (c) hypotonie; (d) rachitisme ou ostéomalacie vitamino-résistants; (e) urolithiase et néphrocalcinose; (f) parfois, comme de Toni y a insisté, obésité et paralysies hypopotassémiques.[5] Les signes urinaires et sanguins sont ceux de l'acidose tubulaire hyperchlorémique avec pH urinaire élevé. Il s'y joint, ce qui est souvent oublié, un trouble de concentration des urines et une hypokaliémie fréquente. La calcémie est normale et la calciurie très élevée; la phosphatémie est basse et la phosphatasémie alcaline est élevée. La surcharge acide au chlorure d'ammonium, capitale pour affirmer l'affection, montre les anomalies portant à la fois sur l'acidogénèse et l'ammoniogénèse.

Certaines difficultés de diagnostic sont maintenant bien connues chez l'enfant: (a) absence d'atteinte osseuse;[10] (b) type sans néphrocalcinose ni lithiase qui simule un diabète insipide néphrogénique avec trouble de l'ammoniogénèse, comme nous l'avons observé avec Debré et Lestradet;[3] (c) test de Sulkowitch négatif malgré l'hypercalciurie en raison de la dilution urinaire.

Pour le pédiatre, il est intéressant de retenir que le mème tableau s'observe secondairement aux malformations congénitales des voies excrétrices d'une part, aux urétéro-sigmoïdostomies pour exstrophie vésicale d'autre part.[22]

Le traitement des formes primitives ou secondaires de ce "rachitisme rénal" tubulaire hypercalciurique est simple. La vitamine D, même à très haute dose, y est peu active. Par contre, l'administration d'un régime sans chlore et la prescription de citrate ou de bicarbonate de sodium ont un effet remarquable sur le rachitisme, la croissance et l'état général; un effet nul sur la néphrocalcinose et sur le défaut de concentration des urines. Ce traitement est à maintenir, tout arrêt entraînant une rechute du rachitisme.

Nous avons discuté avec Prader[22] l'importance du régime sans chlore; à lui seul, il suffit parfois à rééquilibrer ces malades, sans utiliser le citrate; par contre, ce dernier à lui seul permet rarement une correction totale de l'hyperchlorémie.

Nous avons récemment étudiés, chez l'enfant, deux cas de rachitismes vitamino-résistants hypercalciuriques. L'hypercalciurie était isolée, sans hyperparathyroïdie, ni hypercalcémie, ni acidose pustulaire: l'ammoniogènese était normale. Il semble s'agir d'une hypercalciurie rénale primitive, du type de celle décrite par Albright chez les lithiasiques.

(b) *Les "rachitismes tubulaires complexes"*

Les insuffisances tubulaires complexes s'observent en pédiatrie dans des conditions variées: les unes sont secondaires à des néphropathies acquises de l'enfant (telles les observations d'intoxication saturnine de Chishom et de Jean,[2, 11]) ou à des malformations des voies excrétrices des urines, ou à des maladies héréditaires du métabolisme (cystinose, dégénérescence hépatolenticulaire, galactosémie); les autres sont primitivement tubulaires et réalisent des tableaux variés tels que le syndrome de de Toni-Debré-Fanconi idiopathique ou le syndrome oculo-cérébro-rénal de Lowe.[22] Dans ces cas, nous avons observé des rachitismes vitamino-résistants dont le mécanisme est ambigu et peut combiner deux troubles: hypercalciurie par acidose tubulaire et diabète rénal des phosphates. Dans chaque cas particulier, il convient de faire la part de chacun de ces éléments: l'appréciation de la calciurie, l'épreuve de surcharge au chlorure d'ammonium, la mesure du coefficient de réabsorption tubulaire des phosphates sont alors utiles. Certaines affections comme la cystinose s'accompagnent plus volontiers d'hypocalciurie; d'autres, comme le syndrome de de Toni-Debré-Fanconi idiopathique, d'hypercalciurie (Dent et Harris[4]). Mais ces éléments peuvent varier au cours de l'évolution chez un mème malade.

Or la conduite thérapeutique dépend très exactement du trouble tubulaire en jeu. Le plus souvent, il associe dans ces cas: diabète rénal phosphaté et acidose tubulaire. Le traitement doit, en conséquence, reposer sur l'utilisation combinée: du régime sans chlore, de bicarbonate ou de citrate de sodium, de vitamine D à dose massive. Nous procédons en trois temps en raison de la possibilité, assez exceptionnelle en vérité, de déclencher chez ces enfants, avec la thérapeutique alcalinisante, des hypokaliémies graves.[22] Le premier temps consiste à administrer le bicarbonate ou le citrate de sodium de façon à réduire l'acidose et l'hypercalciurie; le second temps, à prescrire du citrate de potassium si la kaliémie s'abaisse; le troisième temps, à donner 0.5 mg. par jour de vitamine D, en adaptant cette dose par la surveillance de la calciurie et de la calcémie.

Le résultat, sur ce type de rachitisme vitamino-résistant, est bon, médiocre ou nul: là encore, le traitement ne doit pas être interrompu sous peine de rechute. Il n'est pas rare que, lorsqu'elles existent, la glucosurie et l'hyperamino-acidurie disparaissent sous l'effet de ce traitement pour des raisons peu claires.

(2) LES OSTÉOPATHIES DECALCIFIANTES DE L'INSUFFISANCE RÉNALE GLOBALE

Il est généralement admis que l'insuffisance rénale globale de l'enfance avec hyperazotémie, acidose, hyperphosphatémie et hypocalcémie entraîne des lésions squelettiques, autrefois dites "rachitisme rénal", qui en réalité sont liées à une ostéodystrophie par hyperparathyroïdisme secondaire: l'aspect grignoté et microkystique des images radiologiques, les lésions d'ostéite fibreuse ou fibrokystique avec ostéoclasie intense, la constatation nécropsique d'hyperplasie des parathyroïdes forment à cet égard un ensemble cohérent. Ce type est donc à exclure des rachitismes.

Cependant, là encore, des nuances sont nécessaires.

(a) La coupure entre les insuffisances tubulaires créatrices de rachitismes rénaux et les insuffisances glomérulaires engendrant l'ostéodystrophie hyperparathyroïdienne ne s'inscrit pas aussi nettement dans les faits que dans les textes. Les néphropathies chroniques de l'enfant sont souvent mixtes; le retentissement squelettique est variable; les biopsies squelettiques, à côté de lésions pures de rachitisme ou d'ostéite fibrokystique, nous ont montré, ainsi qu'à d'autres auteurs, des associations de ces deux types ou même des lésions inclassables.

Un des faits les plus intéressants à cet égard est de voir se succéder, au cours de l'évolution d'une néphropathie donnée, un rachitisme tubulaire, puis une ostéodystrophie hyperparathyroïdienne. Nous avons saisi cette succession chez un enfant atteint de cystinose, chez un autre présentant une néphropathie secondaire à un méga-uretère congénital. Il nous arrive ainsi de discuter les "ostéodystrophies de passage" chez des enfants présentant déjà une urée sanguine élevée et une clearance glomérulaire basse, mais aussi une acidose hyperchlorémique et parfois une hypercalciurie.

(b) En vérité, les études radiologiques et histologiques du squelette montrent beaucoup plus souvent dans ces cas une *ostéomalacie* avec douleurs et stries de Milkman, qu'une ostéite fibro-ostéoclasiante (en dépit d'une hyperplasie parathyroïdienne qui est constante), décalcification qui peut être localisée ou régionale.

Les études faites chez l'adulte montrent, dans l'insuffisance rénale globale, des faits que nous avons retrouvés en partie chez l'enfant: (1) une hypocalcémie et une hyperphosphatémie fréquentes mais inconstantes, une hypophosphaturie et surtout une hypocalciurie constantes; (2) les épreuves dynamiques sont celles de l'ostéomalacie: fixation exagérée du calcium injecté dans la veine, calciurie non modifiée par cortisone et vitamine D; (3) le bilan calcique montre l'augmentation du calcium fécal qui peut dépasser de 200 mg. ou plus le calcium alimentaire. La vitamine D abaisse nettement le calcium fécal.

La présence d'une hypercalciurie au cours d'une insuffisance rénale globale doit faire penser à une insuffisance tubulaire associée ou à une maladie osseuse juxtaposée.

(3) DIAGNOSTIC DIFFÉRENTIEL

Un problème difficile de diagnostic est posé par des affections juxtaposant des signes squelettiques et rénaux et qui ne sont pas des rachitismes rénaux vitamino-résistants.

La première est *le rachitisme commun par hypovitaminose D*. Il est bien connu actuellement que celui-ci peut s'accompagner de signes d'insuffisance tubulaire: hyperamino-acidurie, acidose hyperchlorémique[18] et même melliturie. Ces signes tubulaires sont améliorés ou guéris par la vitamine D, comme les anomalies squelettiques.

La seconde est l'aphosphatasie congénitale, connue depuis les travaux de Rathburn en 1948[16] et de Sobel en 1953.[25] D'assez nombreuses observations en sont connues.

La plupart du temps, l'affection frappe des nourrissons qui présentent un craniotabès, des déformations cliniques et radiologiques de rachitisme grave, un état général médiocre. Les signes d'insuffisance rénale et de néphrocalcinose sont habituels et secondaires à la maladie osseuse.

Les anomalies biochimiques sont très caractéristiques: calcémie le plus souvent élevée, phosphatémie élevée et surtout taux nul ou très bas des phosphatases alcalines.

L'évolution est très grave: la mort survient précocement dans l'insuffisance rénale, certains cas s'améliorent, d'autres présentent une craniosténose précoce avec hypertension intracrânienne.

Des formes tardives ont été décrites, réalisant chez le grand enfant une ostéoporose avec genu valgum et une chute prématurée des dents de lait. La fonction rénale est normale.

La compréhension de l'affection est difficile. Schlesinger *et al.*[23] estime qu'il y a une insuffisance d'ostéoblastes dans l'os. D'autres pensent, comme Malbrain, Ponlot et Denys,[15] que le déficit en phosphatase alcaline est généralisé et explique peut-être certaines anomalies rénales. Un argument supplémentaire en faveur d'un trouble métabolique osseux a été découvert par McCance, Morrison et Dent: la forte élimination urinaire de phosphoéthanolamine dans ces cas.[13]

La nature héréditaire de l'affection ne fait aucun doute. Le diagnostic a été fait par radiographie avant la naissance dans un cas familial. La maladie se manifeste assez souvent, mais non toujours chez les parents, par l'existence d'une baisse isolée du taux des phosphatases alcalines du sérum sans traduction clinique.

La vitamine D, même à doses massives, est dépourvue d'action dans ces cas. Il semble même qu'elle soit néfaste, exagère l'hypercalcémie et favorise le développement de la néphrocalcinose, de l'acidose et de l'insuffisance rénale.

Par contre, depuis 1956, plusieurs améliorations intéressantes ont été signalées grâce à l'A.C.T.H. (de Toni et Durand)[6] et à la cortisone (Fraser et Malbrain).[8, 15]

C. *Rachitismes vitamino-resistants primitifs*

Deux types ont retenu notre attention dans ces dernières années.

(1) RACHITISME NON SENSIBLE À LA VITAMINE D DE L'EXTRÊME PRÉMATURÉ

Certains prématurés, nés avec un poids aux environs de 1000 g. présentent aux environs de la sixième à la huitième semaine une ostéomalacie avec fractures multiples non prévenue et non guérie par les doses usuelles de vitamine D. Ce type de rachitisme chez l'extrême prématuré alimenté au lait de femme est attribué au déficit du lait de

femme en calcium par rapport aux besoins très importants de ces enfants. Dans deux observations récentes, nous avons mis en évidence l'existence d'un retard de maturation de la fonction tubulaire de réabsorption du phosphore: le pourcentage de réabsorption tubulaire du phosphore filtré, après blocage parathyroïdien par perfusion veineuse de gluconate de calcium, ne redevenant normal qu'après plusieurs mois.

(2) RACHITISME VITAMINO-RÉSISTANT FAMILIAL HYPOPHOSPHATÉMIQUE

McCune,[14] Dent et Harris,[4] Fanconi et Girardet[7] considèrent cette affection comme un second type très pur de "rachitisme rénal" lié à une anomalie tubulaire des transferts de phosphate. D'où l'une de ses désignations: diabète rénal phosphatique familial.

Il ressemble au rachitisme carentiel commun. Toutefois, plusieurs caractères permettent de l'en différencier. Son début est tardif, dans le courant de la deuxième année ou au-delà. Son tableau clinique s'en écarte par l'importance du nanisme, l'absence d'hypotonie musculaire et de tétanie, l'existence éventuelle d'un faciès particulier et d'anomalies associées: crâniosténose, alopécie précoce, albinisme. La nature héréditaire de l'affection est certaine; elle se transmet suivant le mode dominant simple ou lié au sexe. Au point de vue biologique, il n'y a pas d'hyperamino-acidurie. L'évolution est chronique, devient latente entre 20 et 40 ans pour reprendre, soit à l'occasion de grossesse et de lactation, soit après la quarantaine. Enfin, un dernier caractère distinctif: la résistance aux doses habituelles de vitamine D.

La traitement repose sur l'utilisation continue, jusqu'à la phase de quiescence spontanée, de vitamine D à doses massives: 0.5 à 10 mg. par jour. La dose varie suivant les familles atteintes. On la calcule pour faire remonter au maximum la phosphatémie, rarement en vérité au dessus de 30 mg./l. tout en maintenant la calcémie inférieure à 115 mg./l.

Les ostéotomies de redressement complètent ce traitement. Fait remarquable, l'immobilisation entraîne, sans doute par suite des mouvements calciques, une amélioration générale du rachitisme. Plus même, il convient de stopper à ce moment la traitement vitaminique, sous peins de voir apparaître de graves accidents d'intoxication par la vitamine D.[22]

Cette affection, dont nous avons repris l'étude récemment avec Lamy *et al.*[12] paraît ainsi réaliser un rachitisme rénal tubulaire "hypocalciurique" s'opposant au syndrome d'Albright.

L'explication de la physiopathologie du rachitisme vitamino-résistant hypophosphatémique idiopathique est encore débattue.[12] Trois hypothèses ont été faites: (1) trouble primitif de la trame protéique de l'os; (2) anomalie intestinale primitive de l'absorption calcique que traduit bien, lors des bilans, l'hypocalcie fécale; (3) diabète rénal primitif des phosphates dont la preuve majeure serait l'élévation de la clearance des phosphates.[7] Toutefois, cette clearance élevée des phosphates peut être considérée ou comme un phénomène rénal intrinsèque, ou comme la conséquence secondaire d'une hyperparathyroïdie secondaire à un trouble primitivement osseux ou intestinal. Dans l'espoir de trancher ce débat, nous avons utilisé avec H. Lestradet et D. Jacob, l'épreuve de perfusion veineuse de calcium préconisée par Howard.[20, 21] Nous donnons ici les résultats obtenus sur l'incidence: (1) du taux de rétention calcique; (2) du pourcentage de réabsorption tubulaire des phosphates.

Nous avons étudié huit enfants, dont l'âge s'étale de 3 à 16 ans, atteints de rachitisme vitamino-résistant hypophosphatémique idiopathique caractéristique au point de vue clinique, radiologique et évolutif. Le premier cas était sporadique; les autres étaient familiaux et se transmettaient suivant le type dominant. Le taux de filtration glomérulaire et les transferts tubulaires, mis à part les phosphates, étaient normaux chez tous: seuls deux enfants, les cas 1 et 7 présentaient une hyperamino-acidurie.

Nous avons perfusé chez nos malades, par voie veineuse, en trois heures: 13 mg./kg. de poids de calcium sous forme de gluconate de calcium à 10% mélangé de soluté glucosé à 5%. Rappelons que dans ces conditions, chez le sujet normal: (1) 60 à 75% du calcium perfusé est retenu par l'organisme dans les neuf heures suivant le début de la perfusion calcique; (2) au cours de la première journée de l'épreuve, on observe une rétention de phosphate, une élévation des phosphates du sérum et une élévation du pourcentage de réabsorption tubulaire des phosphates sous l'influence, pense-t-on, d'un freinage parathyroïdien provoqué par l'hypercalcémie.

La technique de l'épreuve comporte une étude du sang et de l'urine portant sur des échantillons de deux jours témoins avant et un jour témoin après l'épreuve; le jour de l'épreuve, sur deux échantillons témoins avant la perfusion et trois échantillons témoins après; pendant la perfusion sur les trois échantillons prélevés pendant la première, la seconde et la troisième heure de la perfusion.

On étudie, pour chacune de ces périodes, la concentration sérique du calcium, du phosphore et de la créatinine et l'élimination urinaire du calcium, du phosphore et de la créatinine. On calcule à partir de ces données: le taux de fixation du calcium perfusé, la clearance du phosphore, la clearance de la créatinine endogène, le pourcentage de réabsorption tubulaire du phosphore filtré et le rapport phosphore/créatinine urinaire.

Les résultats ont été les suivants

(1) *Taux de rétention calcique*: nos malades ont retenu, pendant les neuf heures suivant l'épreuve: 74, 77, 81, 92, 83, 63, 82 et 90% du calcium perfusé. Si l'on considère qu'un enfant normal retient le

TABLEAU I.—RACHITISMES VITAMINO-RÉSISTANTS HYPOPHOSPHATÉMIQUES IDIOPATHIQUES

Noms	Age (ans)	Perfusion intraveineuse de calcium (13 mg./kg./3 heures) Taux de rétention calcique	% de P réabsorbé avant perfusion	% de P réabsorbé après perfusion	Rapport P/Créatinine dans l'urine avant perfusion	Rapport P/Créatinine dans l'urine après perfusion
1. G.Les.....	9	90 p. 100	85	96	0.95	0.13
2. F.Fos.....	7	83 p. 100	86	96.8	1.04	0.22
3. J.C.Wol.....	3	81 p. 100	72	87	1.26	0.52
4. M.Far.....	15	83 p. 100	87	97	0.47	0.14
5. M.D.Rio.....	5	63 p. 100	70	95	1.42	0.23
6. D.Mar.....	16	73.3 p. 100	84.2	48	0.60	2.44
7. E.Gie.....	4	78 p. 100	69	49	1.26	1.90
8. J.M.Nie.....	5	92 p. 100	69	32	0.83	1.81

jour de l'épreuve 60 à 75% du calcium injecté, ces résultats se situent dans la zone normale ou supérieure à la normale.

(2) *Pourcentage de réabsorption tubulaire du phosphore filtré.* Les résultats présentés au Tableau I nous permettent de répartir nos malades en deux groupes.

Chez cinq malades (nº 1, 2, 3, 4 et 5), le pourcentage de réabsorption tubulaire du phosphore est abaissé avant l'épreuve (le chiffre normal étant 90 à 95%) et augmente fortement pendant l'épreuve. Le rapport phosphore/créatinine urinaire s'abaisse nettement après perfusion calcique.

Chez trois malades (6, 7 et 8) au contraire, le pourcentage de réabsorption du phosphore, déjà bas avant l'épreuve s'abaisse très nettement pendant la perfusion de calcium et le rapport urinaire phosphore/créatinine s'élève.

Ces résultats répondent en partie aux questions posées.

(1) Le taux de rétention calcique élevé témoigne d'une avidité osseuse pour le calcium et non d'un défaut de fixation. Ce fait semble éliminer un trouble primitif de la trame protéique de l'os, bien qu'il ait été observé dans la maladie de Paget.

(2) Le premier groupe de malades se comporte comme si la perfusion calcique avait bloqué une hyperactivité parathyroïdienne et avait permis ainsi à la réabsorption tubulaire du phosphore de se faire normalement. En tout cas, le fait que le pourcentage de réabsorption tubulaire du phosphore puisse redevenir normal dans ces conditions rend peu vraisemblable l'existence d'un diabète rénal phosphaté primitif. Dans un des cas qui s'accompagnait d'une hyperamino-acidurie, celle-ci a disparu sous perfusion calcique pour reparaître le lendemain (cas nº 1).

(3) Le second groupe de malades (6, 7, 8) pose un problème plus complexe. L'apparition d'une augmentation de l'élimination urinaire du phosphore peut s'expliquer par le fait que lors de l'injection de calcium, il se produit probablement un passage important de phosphore du milieu cellulaire dans le milieu extracellulaire d'où l'augmentation de la phosphatémie et du phosphore filtré.

La baisse du pourcentage de réabsorption tubulaire du phosphore filtré peut alors s'expliquer de deux façons: (a) ou bien la maladie est la même que pour les sujets du premier groupe, mais son degré, ainsi que celui de l'hyperparathyroïdie réactionnelle est plus accentué, rendant insuffisante l'action freinatrice de la perfusion calcique sur la parathyroïde; (b) ou bien la maladie est primitivement rénale dans ce cas, et il s'agit bien d'un diabète rénal phosphaté primitif. En outre, dans le cas où existait une hyperamino-acidurie celle-ci n'a pas disparu sous perfusion calcique. Nous pensons que la première hypothèse est la plus vraisemblable, car de nouvelles épreuves de blocage faites avec des doses triples de calcium nous ont permis de voir, dans le groupe également, remonter à la normale, le pourcentage de réabsorption tubulaire du phosphore.

Ces résultats suggèrent que: (1) le rachitisme vitamino-résistant hypophosphatémique idiopathique n'est sans doute pas une ostéopathie primitive; (2) est peut-être, mais non certainement, dans une partie des cas, un diabète rénal primitif des phosphates; (3) est certainement dans une autre partie des cas, une maladie non primitivement rénale, que les résultats des bilans calciques conduisent à considérer comme probablement liée à une absorption intestinale défectueuse du calcium.

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DIAGNOSIS OF STAPHYLOCOCCAL ENTERITIS*

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DURING RECENT years considerable evidence has accumulated incriminating the staphylococcus as an important causative factor in a number of types of human enteritis other than staphylococcal food poisoning. This organism would appear to be involved in certain cases of acute pseudomembranous enterocolitis and associated with the development of less severe diarrhœal disease in considerable numbers of patients during the course of treatment with antibiotics.

Considering the fact, however, that most workers agree that staphylococcal enteritis presents no pathognostic clinical features which allow its unequivocal definition, one becomes increasingly disturbed by the lack of a critical approach to the diagnosis of this disease. Two factors are commonly emphasized in various series of cases described in the literature, namely, a history of exposure to an antibiotic and isolation of staphylococci from the stool. Indeed, in many instances, staphylococcal enteritis is defined, by implication, as any post-antibiotic diarrhœa in which antibiotic-resistant staphylococci can be demonstrated in the stool, a concept which has little foundation in fact.

The frequency with which coagulase-positive staphylococci may be found as part of the normal fæcal flora still does not appear to be widely appreciated. A recent survey carried out in this laboratory revealed an intestinal carrier rate of 17% in adult patients without intestinal disease, a value which was observed to rise to over 40% in another group of patients under the influence of prolonged hospital residence and the administration of antibiotics. The carrier rate in infancy was shown to be even more striking, varying between 40 and 80%, depending upon the factors of age, hospital contact and exposure to antibiotics.[1] These results are substantially similar to those reported by other workers.[2-4]

The simple demonstration of pathogenic staphylococci in the stool of a patient would appear, in the face of this carrier rate, to have very limited diagnostic significance. It is not, however, without value. A number of investigators have commented on the observation that in clearly defined cases of severe staphylococcal enteritis, the staphylococcus may be present in very large numbers in the stool, in some instances almost in pure culture. During the course of the carrier study noted above, 19 patients were seen in whom such a heavy staphylococcal intestinal flora was observed. In all of these patients Gram-positive cocci were seen in the direct smear of the stool and coagulase-positive staphylococci were readily isolated on a non-selective medium such as blood agar. It was thought useful to summarize and discuss these cases in order to evaluate this laboratory finding.

CASE REPORTS

CASE 1.—A male patient, aged 33, underwent operation for a perforated appendix with generalized peritonitis. Oxytetracycline, penicillin and streptomycin were administered, and the postoperative course was uneventful until the sixth day, when severe diarrhœa suddenly developed. Despite vigorous supportive therapy, which included the use of chloramphenicol and no less than 15 litres of intravenous fluids, a fatal termination was reached only 16 hours after the onset of diarrhœa. Post-mortem examination revealed an extensive pseudomembranous enterocolitis, and staphylococci were easily demonstrable in sections of both large and small bowel.

CASE 2.—An infant, aged 6 months, with megacolon, was admitted for colectomy. Fever developed postoperatively, and penicillin and streptomycin were administered. The response, however, was poor, and oxytetracycline was started on the fourth postoperative day. Two days later, bowel sounds were first detected, and the next day watery stools were passed, all containing acute inflammatory cells and large numbers of staphylococci. The diarrhœa became progressively worse. On the eighth day previous drugs were discontinued and chloramphenicol started, the organism isolated being sensitive to this drug but resistant to penicillin, streptomycin, tetracycline and erythromycin. A minor response was seen but fluid and electrolyte balance was found very difficult to control, and the patient died on the tenth day. Post-mortem examination revealed pseudomembranous enteritis with staphylococci colonizing in the bowel wall.

CASE 3.—A 60-year-old woman was admitted semicomatose with meningococcal meningitis. The response to treatment with penicillin, sulphonamide and tetracycline was good until the third day, when fever recurred together with a fulminating choleriform diarrhœa requiring massive fluid and electrolyte replacement. Erythromycin was started and all other antibiotics stopped, but the patient's condition continued to deteriorate for the next 24 hours. When sensitivity tests became available, they indicated that the staphylococcus isolated from the stool was resistant to erythromycin but sensitive to chloramphenicol. Administration of the latter agent was associated with rapid recovery.

CASE 4.—A 68-year-old man was admitted to hospital with a diagnosis of long-standing diverticulitis. A colonic resection was performed and chloramphenicol administered postoperatively. The hospital course was not remarkable until the third postoperative day when severe diarrhœa developed. The original antibiotic was stopped, erythromycin started and with appropriate supportive measures the diarrhœa subsided over the next three days, together with the disappearance of staphylococci from the stool and the appearance of a coliform flora.

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CASE 5.—An infant of 2 months was admitted with meningitis due to *Hæmophilus influenzæ*. Treatment was instituted with sulphonamide and chloramphenicol, and minor improvement was observed over the first three days. Acute diarrhœa then developed and Gram-positive cocci were observed in direct smears of the stool. Streptomycin was added to the medication, largely in a further attempt to control the meningitis, and over the next two days the numbers of staphylococci in the fæces progressively decreased and the diarrhœa subsided. The organism was found to be resistant to chloramphenicol but quite sensitive to penicillin and streptomycin.

CASE 6.—An infant of six months was admitted with staphylococcal meningitis due to an antibiotic-sensitive strain. Treatment with penicillin, sulphonamide and chloramphenicol was associated with a good response until the fifth day, when severe diarrhœa developed. Erythromycin was added to the schedule of treatment: the staphylococci disappeared from the stool and the diarrhœa terminated.

These would appear to be examples readily acceptable as severe cases of staphylococcal enteritis. The development of severe diarrhœa three to six days after initiation of therapy with a broad-spectrum antibiotic associated with the predominance in the stool of a staphylococcus resistant to that antibiotic, is noted as a pattern in every case. The location of the organism in the tissues noted at post mortem in the two fatal cases, and the prompt therapeutic response associated with a decline in the staphylococcal intestinal population when an appropriate antibiotic was administered, can leave little doubt that in these cases the organism isolated was intimately associated with the development of the disease state.

CASE 7.—An 83-year-old man was admitted with diverticulitis and moderate diarrhœa. No staphylococci were isolated from the initial stool. Chloramphenicol was started and the hospital course was unremarkable until the sixth day, when there was an exacerbation of diarrhœa associated with the appearance of large numbers of staphylococci in the fæces. The original drug was stopped and the diarrhœa readily controlled by a neomycin-sulphonamide preparation.

CASE 8.—An erythroblastotic infant, aged 5 days, developed moderate diarrhœa after three days of prophylactic tetracycline therapy. The staphylococci disappeared from the stool, and the diarrhœa quickly resolved after administration of chloramphenicol.

Clearly, all patients with a predominantly staphylococcal intestinal flora do not demonstrate the severe disease noted in the first six cases. Although the pattern in Cases 7 and 8 is similar to that in the first six, the circumstances are not nearly so critical.

CASE 9.—An infant of 3 months was admitted because of acute bronchopneumonia. Moderate diarrhœa developed after seven days of treatment with chloramphenicol. As satisfactory resolution of the pneumonia had been achieved at this time, antibiotic therapy was stopped and the diarrhœa readily brought under control by general measures.

CASE 10.—An infant of 2 months admitted with acute tracheitis developed moderate diarrhœa and a predominantly staphylococcal fæcal flora after two days of penicillin and chloramphenicol therapy. Antibiotic therapy was terminated and the diarrhœa resolved without specific treatment.

CASE 11.—An erythroblastotic infant of 10 days developed diarrhœa after two days of tetracycline therapy. The antibiotic was stopped and symptomatic treatment was followed by a satisfactory response.

CASE 12.—An erythroblastotic infant, 6 days old, developed moderate diarrhœa after three days of chloramphenicol therapy. The antibiotic was stopped, and symptomatic treatment resulted in rapid control of the diarrhœa.

CASE 13.—A 5-month-old infant with acute non-streptococcal pharyngitis received penicillin for two days at home. He was admitted to hospital when moderate diarrhœa developed, and he was found to have an aerobic fæcal flora consisting entirely of coagulase-positive staphylococci. The diarrhœa rapidly resolved under general supportive management.

CASE 14.—An infant of one month developed an acute pharyngitis for which penicillin was given at home. Two days after the onset of the illness moderately severe gastro-enteritis developed, and the infant was admitted to hospital two days later. The penicillin was stopped and the gastro-enteritis treated by general supportive measures.

The preceding six cases are illustrative of instances in which diarrhœa may arise following antibiotic therapy associated with a predominantly staphylococcal fæcal flora and in which adequate management may involve purely general supportive measures and the termination of exposure to the antibiotic in question. All of the organisms isolated were found to be resistant to the antibiotic being given, and in all instances cessation of the diarrhœa was associated with a decline in the numbers of intestinal staphylococci, although they were not eliminated as in the cases in which suitable antibiotics were used in treatment.

Cases 13 and 14 are of some interest. Staphylococcal enteritis is generally considered an iatrogenic disease arising in hospital. Both of these cases demonstrate the development of diarrhœal disease of moderate severity in association with a heavy staphylococcal intestinal population, arising outside of hospital. Further, in both instances the antibiotic used was penicillin, a drug which generally has so little effect upon the intestinal flora that one might justifiably argue that it played no part in the development of the diarrhœa. The following cases would appear to be pertinent.

CASE 15.—A 79-year-old woman was admitted in marked congestive heart failure with a history of acute onset of diarrhœa, which was considered to be a manifestation of her cardiac decompensation together with digitalis toxicity. Her clinical condition improved during the first 24 hours in hospital, after appropriate adjustment of digitalis and diuretics and administration of bismuth and chlorodyne. On the second hospital day, although the diarrhœa had subsided, progressive vascular collapse dominated the picture and the patient died 48 hours after the onset of diarrhœa. Post-mortem examination revealed extensive arteriosclerotic heart disease and evidence of congestive heart failure, together with extensive acute pseudomembranous enterocolitis; the most intensive involvement was seen in the ileum, where the acute inflammatory reaction extended from mucosa to serosa and in which large numbers of staphylococci could be seen. The organism isolated was found to be sensitive to all antibiotics tested. At no time were antibiotics administered to this patient.

CASE 16.—An infant of 6 months was admitted to hospital with severe gastro-enteritis. No antibiotics had been administered. Staphylococci were observed in the direct smears of the stool and isolated in large numbers. No other intestinal pathogens were demonstrable. General supportive measures were instituted together with chloramphenicol therapy, and the diarrhœa was seen to resolve rapidly together with a marked reduction in the numbers of fæcal staphylococci.

CASE 17.—An infant of 2 months was admitted to hospital with acute streptococcal pharyngitis and associated moderate diarrhœa. Examination of the stool revealed virtually a pure culture of antibiotic-sensitive coagulase-positive staphylococci. Administration of penicillin was associated with rapid control of both the throat infection and the diarrhœa.

Clearly a predominantly staphylococcal intestinal flora can emerge in patients not resident in hospital and not under the influence of antibiotics, and in the cases seen, such a flora was associated with diarrhœal disease of varying severity. It is interesting to note that the strains isolated from these patients were found to be sensitive to penicillin, streptomycin, erythromycin, tetracycline and chloramphenicol.

CASE 18.—A newborn infant with spina bifida developed diarrhœa, associated with the appearance of large numbers of staphylococci in the stool, after four days in hospital. General supportive measures were instituted and the diarrhœa resolved. The organism isolated was resistant to penicillin and streptomycin.

CASE 19.—A 50-year-old man with a myocardial infarct developed moderate diarrhœa and a staphylococcal intestinal flora after 29 days in hospital. The intestinal disturbance was managed symptomatically and the resolution of the diarrhœa over the next three days was associated with the appearance of a normal bowel flora containing a small number of staphylococci. The organism isolated was resistant to penicillin, streptomycin, tetracycline and erythromycin.

These cases are of some interest in that the abnormal flora appears to have not only developed without the intervention of antibiotics, but to have also been eliminated without their aid. The strains of staphylococcus involved being acquired in hospital, one is not surprised to note their pattern of antibiotic resistance as opposed to the sensitive strains in Cases 15, 16 and 17.

DISCUSSION

Antibiotics are frequently implicated in the pathogenesis of many cases of staphylococcal enteritis.[5-7] It is generally held that the mechanism involved is a depression of the normal fæcal flora that allows antibiotic-resistant staphylococci to multiply and virtually replace the normal organisms. But there is little evidence to suggest that all post-antibiotic diarrhœas are of staphylococcal etiology.

Further, although fluctuations in the nature of the intestinal flora are far from clearly understood, a great many factors other than administration of antibiotics would appear to be capable of inducing profound alterations. Notable among these are variations in diet. If staphylococcal enteritis always arises on the basis of a disturbance in bowel flora, it would seem reasonable to believe that the disease may occur in individuals who have not been exposed to antibiotics but whose intestinal flora may have been altered by another mechanism. This possibility is illustrated by Case 15, in which there was a fatal termination, and by Cases 16, 17, 18 and 19 in which it was less severe. No history of antibiotic exposure was noted in any of these instances.

The possibility that staphylococcal enteritis may occur in the absence of antibiotic therapy has at least two important implications. Firstly, the attention of clinical investigators concerned with the incidence, diagnosis and management of staphylococcal enteritis would appear to be centred on cases of post-antibiotic diarrhœa and it may be that an important group of cases are being excluded. Secondly, a number of workers have presented evidence supporting the view that the incidence of pseudomembranous enterocolitis has not increased since the introduction of the broad-spectrum antibiotics.[8, 9] Unfortunately, this valuable evidence has been frequently interpreted to mean that antibiotics and the staphylococcus are not important factors in the causation of this lesion. This interpretation can be subjected to serious criticism. Pseudomembranous enterocolitis probably does not represent a specific lesion but a reaction to acute and severe intestinal injury that may be produced by a number of factors, only one of which is the staphylococcus. Further, a proportion of the cases occurring in the pre-antibiotic period may well have been of staphylococcal etiology. The lack of appropriate bacteriological studies precludes the possibility of comparing the relative incidence of severe staphy-

lococcal enteritis over various periods of time when using cases derived from older records.

Aside from the above considerations, careful studies of staphylococcal enteritis are markedly handicapped by our lack of understanding of the pathogenesis of this disease. The high carrier rate in normal individuals would appear to indicate that the mere presence of the staphylococcus in the intestinal tract is not sufficient to cause any intestinal disturbance. Indeed, even the distinctly abnormal circumstance of an almost purely staphylococcal intestinal flora is not associated with uniformly severe disease.

A large number of different factors have been recorded as being associated with the development of pseudomembranous enterocolitis.[9-12] Shock, various degrees of intestinal obstruction, thrombosis of capillaries in the intestinal mucosa and pantothenic acid deficiency have all been incriminated. The possibility exists that one or more mechanisms may produce this lesion; that these mechanisms may operate alone or may cause a disturbance of intestinal flora so that the staphylococcus can arise and further aggravate the condition; or that staphylococcal flora may arise owing to the intervention of antibiotics and produce enteritis in conjunction with other factors which devitalize the intestinal mucosa.

A good many cases of severe enteritis, however, would appear to be associated with only one causative factor, the staphylococcus. The fact that there is not an absolute correlation between the numbers of organisms in the intestinal tract and the severity of the disease would suggest that all pathogenic staphylococci are not equally capable of producing acute injury in this site. The nature of such "enteritis-producing" strains is not clear. Surgalla and Dack[13] have claimed that 30 out of 31 strains causing enteritis produced staphylococcal enterotoxin, and suggest that the disease is due to strains producing this particular toxin *in vivo*. Other workers hold the view that severe cases of staphylococcal enteritis involve overwhelming local infection and do not present a picture compatible with acute entero-toxæmia.[14]

The host factors involved in the pathogenesis of staphylococcal enteritis thus remain undefined. The one character of the pathogenic staphylococci which has been claimed to mark "enteritis-producing" strains, namely enterotoxin production, cannot at the present time be subjected to routine test, and the clinical picture has no remarkably distinguishing features. The one routine laboratory procedure which is available is the direct examination of the stool and culture for staphylococci. Admittedly this is an imperfect tool and must be interpreted with caution.

One would suggest that the absence of staphylococci from the stool of a patient suspected of suffering from staphylococcal enteritis would tend to deny the diagnosis.

The presence of staphylococci in the stool of such a patient, considering the significant carrier rate, does not conclusively make the diagnosis but merely indicates that the patient belongs to the statistical group in which cases of staphylococcal enteritis are seen. Consideration must be given, in the management of such a patient, to certain practical factors. Vigorous antibiotic therapy may be life-saving in severe staphylococcal enteritis. Thus in severe diarrhœal disease, if staphylococci were demonstrated in the stool, one would feel impelled to use a suitable antibiotic although the diagnosis is not proved. In moderate to mild cases, however, one would feel justified in upholding the principle of the reservation of specific treatment until a specific diagnosis has been made and temporizing by discontinuing any offending antibiotic and by using general supportive measures. Many observers believe that mild staphylococcal enteritis will resolve without specific treatment. It is further our impression that severe staphylococcal enteritis tends to present abruptly and not as a progressive development of mild to severe diarrhœa over several days. Temporization with mild cases suspected of being staphylococcal enteritis would appear to us to be perfectly justified, unassociated with significant risk, and a way of avoiding unnecessary exposure to antibiotics.

Demonstration of coagulase-positive staphylococci in the stool in very large numbers, i.e. predominantly Gram-positive cocci in the direct smear and the organism easily isolated on a non-selective medium which would ordinarily be overgrown by coliform bacteria, adds a further dimension to the assessment. A predominantly staphylococcal fæcal flora is, in our experience, a distinctly abnormal finding invariably associated with diarrhœa of varying severity. This is a laboratory finding deserving of considerable respect and one which would incline one to a diagnosis of staphylococcal enteritis and the institution of chemotherapy.

The specific diagnosis of staphylococcal enteritis clearly must await definition of the pathogenesis of this disease. Until such time, careful assessment of stool cultures for staphylococci would appear to be of considerable practical value.

SUMMARY

During the course of a study of the staphylococcal intestinal carrier rate some 19 patients were seen in whom a predominantly staphylococcal intestinal flora was observed. The histories of these patients are presented and it is observed that in all cases the abnormal flora was associated with diarrhœal disease, varying, however, from fatal pseudomembranous enteritis to minor diarrhœa. The development of such an intestinal flora, although commonly associated with antibiotic therapy in hospitalized patients, is shown to be not restricted to such individuals but may arise in non-hospitalized patients and in those not exposed to antibiotics. The interpretation of stool cultures for staphylococci and the diagnosis of staphylococcal enteritis are discussed.

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Special Article

MODERN TREATMENT FOR MENTAL ILLNESS*

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PART II OF TWO PARTS

THE PRINCIPLES which should be followed in connection with the location and development of a comprehensive community mental hospital are worthy of consideration. However, it is first necessary to consider the services to be provided by such a facility and the essential attitudes which a community must have for its successful operation.

The golden rule, "Do unto others as you would that they should do unto you", illustrates in a straightforward way some of the fundamental issues which must be solved. To appreciate the needs of the mentally ill, one must first of all think of the needs of any sick person. One must appreciate the anxiety which exists—for patients and their relatives—when illness strikes, and the need for comfort during such difficult times. For a person with an acute physical illness we provide hospitals readily accessible to the community, families and friends, and during periods of acute illness we allow almost unrestricted visiting. In the case of the mentally ill such facilities do not usually exist and the patient while acutely disturbed and anxious is frequently transferred to a hospital some twenty, fifty or even hundreds of miles from his home. Possibly this is not too important during the first few hours or even days, but as patients begin to respond to treatment they become confused and feel lost because they are unable to have the necessary contact with their families.

During recent years several plans in the direction of community mental hospitals have been announced. Some of us have been urging this for many years. We hope that some of the provinces will provide the necessary leadership and stimulate the desire for similar developments across this country.

When a person is physically ill, we extend a helping hand and do everything possible to make him comfortable. In the case of mentally ill persons, they are too often dealt with by the law or by an untrained staff who act as attendants or guards and who frequently lock patients up because they are "sick", rather than taking steps to deal with the symptoms which are present. When a patient is convalescing from a physical illness, visits from members of the family, friends and fellow workers are welcomed and the patient is encouraged to spend increasing periods of time visiting at home and elsewhere in the community. In the case of mental illness, the geographical location of the hospital frequently makes this impossible. Thus it seems almost unnecessary to state the first important principle which must be observed in the development of a comprehensive community mental health service, namely, the hospital must be located in the community it serves.

This concept of a community mental hospital is exactly the same as the concept of the community general hospital. The fact that this principle has not been readily accepted cannot be attributed to such extraneous factors as the alleged extra cost of small hospitals. If this were the case, we would not have developed the community general hospitals of which this country is so justly proud. In fact, there is no proof that hospitals from three hundred to five hundred beds are not the most economical. All figures indicate that hospitals over that size are much more expensive. Some of this extra cost is due to the development of costly and special services, but much of it may be due to the multiplication of administrative and technical services and to inefficiency related to our inability to utilize and supervise staff properly in such large organizations. One has only to spend a short time in the lobby or elevator area of a large general hospital to realize how much staff time is lost in simply getting from place to place, and one also begins to realize the extensive duplication of services which becomes necessary to make these monolithic structures function at all. So far as large mental hospitals are concerned, there seems to be no justification for comparing their *per diem* costs with those of a community mental hospital, as there is so much wrong with the existing hospitals, there are so many deficiencies, and the treatment provided is so inadequate that any suggestion of using their costs for comparative

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purposes is beyond comprehension. Experience with active treatment indicates that the cost of each patient treated may well be lower in the community mental hospital than in the traditional mental hospital. The reason we do not have these hospitals is not the cost, but is due to a failure to understand the need for them, and because we in the community have not yet developed a proper attitude towards the mentally ill.

The community hospital will not be successful if it is placed on some farm near the city. It must be in the city, of the city and easily available by general public transportation. The developing concept of the community mental hospital would, perhaps, be more readily understood if it were described as a community mental health centre, from which a number of community mental health services would be provided and in relation to which many other existing and proposed services would be coordinated. This being the case, it is apparent that geographical location is of the utmost importance. There are a number of studies which indicate clearly the importance of distance as a factor in the utilization of health services, e.g. it has been shown that the admission rates to hospitals are almost directly proportional to the distance from hospital. A study in Minnesota indicated that patients can seldom arrange to travel more than one hour in each direction in order to utilize a psychiatric service.

HOSPITAL DESIGN

As the community mental hospital has to provide a range of services extending from consultation, outpatient treatment, day and night care and finally to inpatient services, it is apparent that the floor space required for other than bed accommodation will be considerable. It will be considerable not only because of the proportion of ambulatory and day treatment services to inpatient services, but because mental health services are very different from other health services in that the interview is the characteristic method of examination and treatment. Thus practically all the professional workers require individual offices in order to work effectively with their patients. There is in addition a considerable requirement of space for occupational, recreational and activities therapy. As day hospital services develop, the need for cafeteria facilities for day patients becomes marked and may in some cases exceed the need for inpatients. It has been very difficult in the past to convince administrators and architects of these particular needs for space in psychiatric facilities, and many mental health services have been handicapped because too little space was made available for interviews and treatment.

CONTINUITY OF TREATMENT

As efforts have been made to develop more adequate community mental health services, it has become apparent that all treatment must be considered as a continuum. The illness is one illness and must be treated as such whether the patient is from time to time receiving treatment at home, in an outpatient clinic, in a day hospital or as an inpatient. The essential continuity is provided by the staff who look after the patient, and continuity can only be accomplished when the inpatient facilities are located in or are readily accessible to the community where the patient lives. Where such a range of treatment services is available in the community, there is now good evidence that the amount of time a patient spends in hospital can be considerably reduced. Conversely, patients are with their families and in the community for much longer periods of time where they are able to contribute usefully to society rather than being in hospital as non-participating dependent persons.

STAFFING THE HOSPITAL

The staffing of these facilities presents many problems. There appears to be an almost universal shortage of all types of professional workers, and the tendency to separate provincial mental health services from other community services has exacerbated this situation. The effective staffing of these community facilities will require a great deal of flexibility and will almost certainly involve the employment of personnel on sessional and part-time arrangements in addition to the traditional full-time method. Indeed, as continuity of care is of the essence in psychiatric treatment and as it is essential for private practitioners to have access to adequate treatment facilities, there would be additional merit in the involvement of psychiatrists on a sessional basis with the hope that the same physician could be responsible for the patient at home, in office practice, and in the special treatment facility.

VOLUNTEERS

The use of volunteers can be of considerable assistance in the development of these services. While volunteers cannot take the same continuing or professional responsibility as do staff members, they can certainly be of assistance in all areas ranging from clerical duties in the records and appointment areas to occupational and activities therapy. There has been an unfortunate tendency in mental health services to particularize and emphasize the differences between the care of psychiatric patients and others, with the result that some staff have been reluctant to enlist the help of volunteers and some volunteers have been unwilling to assist because they feel they are too uninformed. These matters will require clarification and a good deal of energy will have to be expended in the development of adequate volunteer services if these community facilities are to have their maximum effect. If space permitted, one could discuss in detail the importance of volunteers in quite a different way. For example, it is apparent that the volunteer constitutes a bridge of understanding between the psychiatric services and the community quite beyond the abilities of the professional staff. Also, the volunteers can have and provide a relationship with patients because they occupy a special role in relation to the patient which the staff cannot hope to attain.

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NATURE AND EXTENT OF TREATMENT

Much has been said about the particular services which can be rendered on an ambulatory basis. There are those who would limit ambulatory treatment to psychotherapy and drugs, while others would provide electroconvulsive therapy and still others insulin therapy. It is not desirable to generalize on these matters, as the extent and nature of many complex factors including the condition and understanding of the patient, the responsibility and attitude of the family, and the extent to which supervisory services can be provided to a patient at home must be considered in each case and locality. The important thing to be considered in deciding the extent of treatment to be offered to ambulatory patients is the responsibility of the treating physician. In other fields of medical care, this item is not generally discussed because it is assumed that the attending physician will make the appropriate decision in any given circumstance and he has been left free to do so. Perhaps it is time that the same approach was taken in connection with psychiatric services, and one wonders if psychiatrists would not show greater initiative and assume more responsibility for their patients if they were given the authority to make such decisions on a clinical rather than an administrative basis.

INPATIENT SERVICES

There is some danger in present efforts to compare psychiatric hospital services with general hospital services. There is a tendency to assume that good psychiatric treatment would be available if psychiatric hospital facilities were the same as those provided in general hospitals. Such is not the case! The treatment of psychiatric conditions is quite different from the treatment of physical conditions. Apart from the chronic debilitating physical conditions, general hospitals are usually concerned with short-term illness and the patient's average length of stay in hospital seldom exceeds eight to ten days. If one were to consider the treatment programs of general hospitals in respect of chronic physical illness, one would certainly gain a different picture of the effectiveness of our existing hospital services. The majority of psychiatric patients are ambulatory and their main requirement is for services beyond that provided in their bed or at the bedside. The availability of occupational, recreational and activities therapy is of the essence, and there are those who feel that the availability of space outside the hospital is also of great importance. Many psychiatrists have emphasized the importance of nature and living things in the treatment of psychiatric patients, and those physicians who have had to care for psychiatric patients in psychiatric units of large general hospitals have frequently stressed the difficulties created when there are not sufficient grounds available for patients to spend considerable periods of time devoted to recreation, flower gardening, and so on outside the hospital. In the development of community mental hospitals, this point must be kept in mind and such space must be provided.

THE LONG-TERM PATIENT

It is also necessary to point out the pitfalls inherent in any attempt to separate patients into acute and chronic. There is, however, considerable justification for separating patients into two groups—those who require treatment and those who are socially dependent (i.e. require only custodial care). This latter group of patients—those requiring only custodial care—should not be in hospital at all but should be cared for in domiciliary programs ranging from foster home care through boarding homes to the various types of welfare institutions. As far as health services are concerned, their health needs are no different from the needs of other people living in the community, and their social needs should not be met by a perversion of the functions of health services but by a properly developed and complementary welfare service. There are many patients who suffer from long-term psychiatric illness, but there is good reason to believe that the number remaining in hospital can be considerably reduced when these patients are treated in a small community hospital compared with the results obtained when they are relegated to the back wards of large mental hospitals or to special hospitals for the "chronically sick". There are many mental hospitals in North America today which can report each year the discharge of a considerable number of patients who have been in hospital for periods ranging from five years to 20 years. These are the hospitals in which reorganization of program and fortunate location have permitted them to function along the lines of the proposed community mental hospitals. When the time comes to discharge these patients, the residual problems do not relate to the medical condition from which they suffer but to the social isolation which has been developed and perpetuated between the patient, the family and the community. Many more such patients would be discharged if a closer relationship had been maintained with their families, with the community and with their place of work, and only by accomplishing such objectives can we hope to reduce the resident population of our mental hospitals.

SPECIALIZED MENTAL HOSPITALS

If the community mental hospital is to function adequately, the responsibilities of mental health services must also be clarified. There is too great a tendency in North America for the mental health services to accept responsibilities beyond their capabilities and in situations where they cannot hope, at this time, to contribute to a solution of the particular social problem. Some might say that the mental health services have been forced to accept these responsibilities. Whether they have sought them or have been forced to accept them does not alter the needs which exist. Two groups of patients in particular come to mind at this point, namely, psychopaths and insane criminals. In the former group, there is good reason to believe that a properly developed psychiatrically oriented program may do much to improve the behaviour of such persons, but there comes a time when these people like all others in our society must accept responsibility for their own behaviour. Too many of our mental

hospital programs are distorted because they are expected to care for psychopaths who would be cared for more appropriately in specially developed institutions. The same is true of insane criminals. If a mentally ill person commits a crime specifically related to the illness from which he suffers then he certainly deserves and requires treatment, but whether this should be in a regular hospital or in a specially developed institution is a moot point. Certainly there is no reason to expect mental hospitals to assume responsibility for the custody of persons where the crime was not related to the illness and especially when treatment offers no hope for removing or curing the factors which led to the crime being committed in the first place. While all of these people require treatment, it should not be allowed to interfere with the provision of adequate treatment to sick people who have not so violated our code of behaviour. The time has come in this country when special facilities should be developed for the care of psychopaths and insane criminals. Only when insane criminals and psychopaths are properly segregated in special centres established for their care can we hope to develop mental hospitals in which it will be possible to give proper treatment.

ADMISSION PROCEDURES

There is now good reason to believe that mentally ill people respond better to understanding and to the anticipation of responsible behaviour than they do to the anticipation of disturbed, destructive or antisocial behaviour. Experience with open hospitals in Great Britain and now in North America confirms this belief. If we expect our community mental hospitals to fill their proper role, they must be organized and developed on the principle of no restraint and the development of patient responsibility rather than regressive protective care.

It is also apparent that the majority of mentally ill patients accept treatment when a proper referral is made and that most of these patients should not be certified or committed to mental hospitals. They should be admitted to mental hospitals in the same way as patients are admitted to other hospitals. One has to make provisions for patients whose illness prevents them from accepting treatment, but experience everywhere indicates that this can be accomplished with relatively few legal restraints and the use of appropriate treatment, particularly when this treatment is given in an institution which is designed for treatment and not custody.

It is desirable to clear up the misconceptions which prevail in this country regarding voluntary admissions to mental hospitals. Voluntary admissions as now used in this country are anomalous and do not provide adequately for the admission of a mentally ill person who is willing to have the necessary treatment. When one reads the form which a voluntary patient is expected to sign, one quickly finds that this is little more than a self-committal. It is a form in which the patient agrees to abide by the rules and regulations of the hospital and to give prescribed notice before leaving hospital. This voluntary type of admission has served a useful purpose but it must now be replaced by a true hospital admission in which the doctor requests treatment for the patient and the patient signs consent for treatment with no loss of his personal or civil rights.

ADDITIONAL CONSIDERATIONS

There are a few additional items which must be considered before summarizing the needs for and principles essential to the operation of a community mental hospital.

During recent years there has been considerable emphasis on the provision of more adequate hospital services for the Canadian population on a prepaid basis. When the original federal proposals were made the treatment of the mentally ill was excluded. As a result of many representations the federal offer was amended to provide for the treatment of the mentally ill in general hospitals, but all treatment in mental hospitals continued to be excluded. This action was protested by the opposition of that day and it is regretted that a change of government has not produced the anticipated change for the mentally ill. The exclusion is justified or rationalized on the basis that patients do not pay for mental hospital care, or that such federal payments would only be additional federal financial assistance to the provinces, or the federal government cannot afford to make such contributions, or even the suggestion that too many patients are confined to but not treated in mental hospitals. None of these arguments are valid, and the exclusion of mental hospitals under the federal legislation has perpetuated and indeed emphasized the separation of treatment of the mentally ill from treatment of the physically ill. Generally speaking, legislation—Hospital Insurance, Immigration Act, the original Old Age Pension Act and others—has tended to discriminate against the mentally ill. It seems unreasonable to talk to the mentally ill about treatment and hospital care when they are told that their regular insurance does not cover the costs of their care in mental hospitals. This emphasizes in their minds the fact that their illness is different and that their benefits and rights are not the same as when they suffer from other illnesses. Fortunately, two provinces, Ontario and Prince Edward Island, have provided for coverage in mental hospitals and it is to be hoped that others will follow suit.

HOSPITAL MANAGEMENT

At the risk of incurring the wrath of many good friends in the civil service, it does appear that the mental health services of this country have been stifled by civil service commissions, treasury boards and other government departments. The many problems faced by all of these agencies and the willingness of the individuals in these departments to cooperate are much appreciated, but one must also recognize that government was not designed to operate hospitals or provide personal care services. In Great Britain where health services are nationalized, mental hospitals are operated by regional hospital boards and committees of management, not by government departments. What a difference! It is like comparing our general hospitals with the existing mental hospitals! In the former we see the community demanding superior service;

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we see community leaders in action, and we see progress, initiative and development. In the latter we find many dedicated professional people battling against complacency, lack of interest, lack of community support, and the absence of initiative, development and progress. When action is seen in the mental health field it is almost always in the form of excessive bricks and mortar in the wrong location and made even more ineffective by the failure to provide opportunity and satisfactory identification for the personnel who must look after the patients. In spite of this, many mental hospitals have provided, are providing and will continue to provide good service, but more radical action is necessary.

The development of hospital insurance provides a unique opportunity for experimentation. Is it possible that the mentally ill could be treated under hospital insurance in hospitals operated by the boards of management rather than by government departments? One can predict that such a service would be more flexible, would be freer to experiment with new programs and would be more responsive to community needs. The operation of all of our mental health services by community boards would bring about radical improvement and would be more in keeping with our ideals and ambitions as a democratic country.

ACTION REQUIRED

The development of community mental health services is dependent on a number of factors, amongst the most important of which are:

1. A clear understanding by the community of the needs of psychiatric patients.

2. A complete redrafting of all legislation dealing with mental illness. These revisions should cover the Criminal Code, Immigration and Sick Mariners Legislation, the Hospital Insurance and Diagnostic Services Act, the Penitentiaries Act, the Mental Hospital and related Acts in all of the provinces, and the various curatorship or protection Acts.

3. The development of comprehensive services ranging from consultation and out-patient departments through day and night care to in-patient services based on the in-patient beds of community mental hospitals strategically located throughout the country.

4. Separate facilities for psychopaths, criminals, addicts, the mentally retarded and other special psychosocial conditions.

5. The provision of supporting rehabilitation programs—halfway houses, sheltered workshops, vocational training centres, foster homes, welfare institutions and so on.

6. A meaningful involvement of the community through citizen participation on boards of hospitals, clinics and other services, and extensive expansion of volunteer programs.

7. More adequate research—not only into specific conditions but to assess clinical services and develop new methods of treatment and organization (see 1).

Does the above seem to be too all-embracing? Is it unrealistic? Can we afford it? Must we have all this new legislation? The answers are obvious. One of every twelve to sixteen Canadians born today will be treated in a mental hospital. Some three to four persons in every thousand of our population are confined in mental hospitals. In case doubts still exist some questions are suggested for your further consideration. Perhaps you can answer them immediately. Perhaps you will think about them today or next week. Please don't forget them, because your understanding and support are essential.

How will you feel when one of your children or grandchildren develops schizophrenia? How will you feel when your mother or father can no longer be looked after at home? What will you do when your wife suffers a breakdown? How will your wife feel if you become depressed? Would you want to go to one of our mental hospitals for treatment?

The general hospital units while playing a very important part in our total program cannot take care of all of these illnesses. In spite of all the new and improved services, admissions to our mental hospitals are increasing by 20 to 25% each year. The hospitals could be more effective. Many more patients can be kept well. But further action is necessary. Will you help? Will you look on mental illness as you do any other illness? Will you see that there are jobs for former patients? Will you see that our hospitals are properly located, properly staffed and available and that they are good enough for you, for your wife, for your parents and for your children?

AS OTHERS SAW IT

Now, if a doctor happens to fall from grace so far as to advertise his hours in the lay press, beyond a few days, of course, up goes an execration of an awful texture from an outraged profession. Then why not mete out the same dose to the man who knows in his heart that his [public] lectures are not so much to cater for those requiring the knowledge as to get a chance to rub shoulders with another's bread and butter? Again, why are we expected by the public to be less conservative than lawyers? Their professional training is not more costly than ours. And yet whoever heard of a lawyer—unless he was an inspired idiot, and he is not generally built that way—openly advocating cheap law or shrieking for simplified legal procedures? Then dentists have we, humane and philanthropic no doubt, but do we hear of first-aid lectures on dentistry? And a pharmacist sunk in such utter depravity as to teach the art of dispensing to the great unwashed would be instantly signed up as a dangerous lunatic, and very properly too.—Letter to the Editor, *Australasian Medical Gazette*, July 1899; reprinted in *Australian M. J.*, 1: 392, 1960.

MEDICO-LEGAL

MEDICO-LEGAL ASPECTS OF INTERSEXUALITY: CRITERIA OF SEX*

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PART I OF TWO PARTS

RELATIVELY RECENT developments concerning the criteria of sex have raised questions that have medico-legal implications. Society and the law recognize only two sexes. Usually the differences are obvious, partly because cosmetic and garment manufacturers make it easy for females to accentuate or falsify their characteristics.

At birth the physician assigns sex from the appearance of the external genitalia. If these organs are equivocal, other criteria must be used. In the past a final decision was usually not made until the type of gonads had been determined. Often this was not done until contradictory sex characteristics appeared at puberty; frequently in such cases sex was changed, resulting many times in unhappy confused patients.

During the past decade much has been learned about the diagnosis and management of intersex.[1] New laboratory procedures have made it relatively easy to make a credible diagnosis without exploratory surgery. Sex may now be assigned with confidence fairly soon after birth; corrective surgery and hormone therapy may be carried out later. As a result, intersexes may lead fairly normal lives. Many can be made marriageable; some will be fertile.

MEDICAL ASPECTS OF INTERSEXUALITY

The appropriate sex for an intersex is not always consistent with that established at fertilization or with the type of gonads. Sex in such patients should not be based on any one aspect of sex; all criteria must be considered. In the newborn, special emphasis should be placed on external genital anatomy and on the surgical possibilities of creating functional sex organs. In persons beyond infancy, utmost importance should be attached to the sex that has been adopted; in these cases it is usually best to retain the sex of rearing to prevent psychological maladjustment. Often a person's suitability for a sex may be greatly improved by hormonal therapy and plastic surgery.

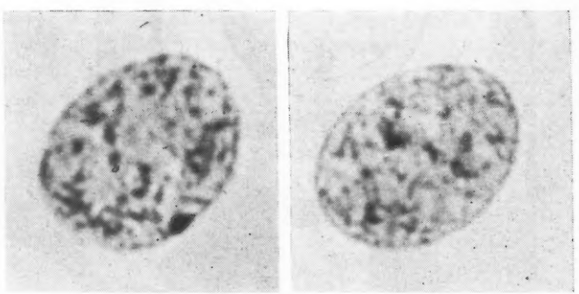
As recently as six years ago, most physicians believed that sex of rearing should, almost invariably, be consistent with gonadal sex. This firm belief often resulted in changes of sex well beyond infancy, sometimes in adults. It may be that unreasonable emphasis as to sex is still placed on gonads by some doctors; certainly this idea is prevalent in non-medical groups. It is, of course, desirable to designate the sex indicated by the gonads, but this may not always be reasonable. There need be no hesitation in raising a person contrary to gonadal sex; it is well established that sex orientation develops according to sex of rearing.[2] Physicians must be able to make accurate judgment in such cases, and be prepared to outline the rationale for such decisions. Knowledge of intersexuality is valuable, not only because of possible legal complications, but in order to prevent tragic and embarrassing mistakes.

Before the various forms of intersexuality are described, the criteria of sex that should be used in forming a correct judgment of appropriate sex will be briefly outlined. The criteria are: (1) chromosomal sex, (2) gonadal sex, (3) hormone pattern, (4) internal sex organs, (5) external genitalia, (6) habitus, (7) sex of rearing, and (8) gender role and orientation. In the newborn, the first five criteria are used.

CRITERIA OF SEX

1. *Chromosomal Sex*

An embryo's chromosomal sex is established at fertilization and depends on whether or not an ovum is fertilized by an X or a Y sperm (Fig. 2). Chromosomal females have two X chromosomes, whereas chromosomal males have an X and a Y chromosome. A person's chromosomal sex can be detected by a chromatin test;[3] the most commonly used is the oral smear method.[4, 5] Nuclei of chromosomal females contain a special mass of chromatin, the sex chromatin (Fig 1a),



a. b.

Fig. 1.—a. Nucleus with sex chromatin in an oral mucosal smear from a chromosomal female. b. Nucleus without sex chromatin in an oral smear from a chromosomal male. (Cresylecht violet, × 3000.)

that is not visible in nuclei of chromosomal males (Fig. 1b). The generally accepted hypothesis is that the sex chromatin represents persistent portions of heterochromatic regions of the X chromosomes. Similar parts of the X and Y chromosomes of males do not form a recognizable chromatin mass in interphase nuclei.[6]

If sex chromatin is visible, it may be inferred that the nuclei contain two X chromosomes. Nuclei of this type should be referred to as chromatin-positive, never as female, for such reference could unnecessarily upset a patient if this criterion indicated the sex opposite to the person's rearing. If cells from an intersex are chromatin-positive, it is also likely that two X chromosomes are present, but the actual chromosome constitution cannot be determined by this method. With new cytological techniques it has been shown that intersexes with chromatin-positive nuclei may have the following sex chromosome constitutions: XX, XXX or XXY.[7, 8] It is important to realize also that the

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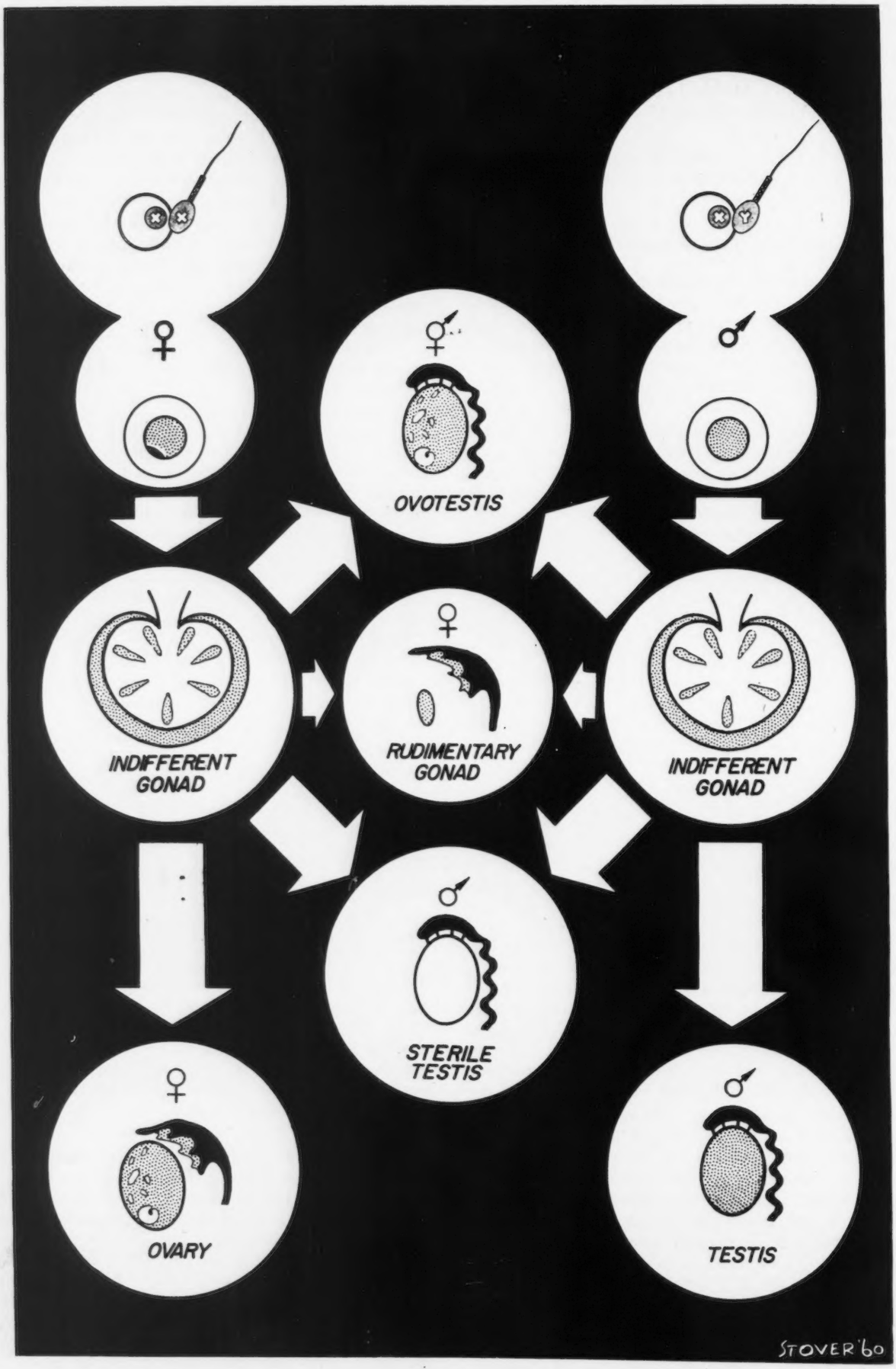

Fig. 2.—Diagrammatic representation of sex determination and differentiation. Normal development is represented in the outside columns; some types of abnormal differentiation are illustrated in the centre column.

chromatin test gives no direct information as to genetic sex; that is, sex gene constitution and arrangement.

If sex chromatin is not visible in a random sample of 100 nuclei, it may be inferred that the XY sex chromosome constitution is present. Cells of this type should be referred to clinically as chromatin-negative. In an intersex this nuclear pattern indicates that two X chromosomes are not present, but it cannot be determined by this method whether the sex chromosome constitution is XY, XO, YO or O. This does not detract from the great practical value of the chromatin test in the differential diagnosis of intersex.[1] Indeed it was the development of a relatively simple method of detecting chromosomal sex that stimulated new interest in intersexuality.[9]

The use of chromosomal sex as the sole criterion of sex would of course be ridiculous. No physician would suggest that a person with the normal appearance of one sex should be raised in the other on the basis of chromosomal sex alone.

2. *Gonadal Sex*

The sex of the gonads apparently depends on the ratio between male-determining and female-determining genes. If the genes for femaleness predominate, ovaries develop, whereas if there is an excess of male-determining genes, testes form. Thus faulty chromosomal distribution and genic abnormalities may cause abnormal gonadal development. Ovaries may develop in chromosomal males, or testes in chromosomal females; these conditions are known to occur in man.[10, 11] In genetic females the cortex of the indifferent gonad differentiates into an ovary and the medulla regresses (Fig. 2); in genetic males, the medulla develops into a testis and the cortex recedes. If there is a genetic disturbance or abnormal hormones are present, both the medulla and cortex may differentiate to form an ovotestis.

Occasionally no gonads form, or more commonly, vestigial structures with ovarian-like stroma develop. This type of gonad may be found in chromosomal males or females, but is commoner in the former.[12] It has been shown that some chromatin-negative patients with this gonadal condition lack a Y chromosome.[13] This and other evidence[14] suggest that the Y chromosome may have an active role in determination of maleness.

3. *Sex Hormone Pattern*

Fetal testes produce hormones or inductor substances that cause masculine differentiation of indifferent sex structures. Failure of testes to form or to produce androgenic hormones results in female development. Thus all fetuses appear feminine, unless masculinizing substances are present.[15] Conversely, masculinization of female fetuses occurs if androgenic substances act on undifferentiated or partially differentiated structures. The common source of such substances in human fetuses is the hyperplastic adrenal. Similar effects may be caused by maternal androgenic substances from masculinizing tumours,[16] or by administered testosterone preparations.[17]

It is particularly important that the hormone status of intersexes be considered. If excessive amounts of androgens are being produced in a female, masculinization will be progressive. At puberty testes in intersexes may produce either androgens or œstrogens; generally if the genitals are ambiguous, testes produce androgens, whereas if the genitals are normal for a female, testes produce œstrogens. Thus gonads in intersex patients may cause embarrassing characteristics to develop at puberty. Signs of contradictory sex development should be watched for around puberty and, if they appear, the condition should be treated before it causes concern.

4. *Internal Sex Organs*

Every fetus has ducts capable of developing into either male or female internal genitalia. If male hormone is present in sufficient quantities at the appropriate time, male organs develop, whereas if it is absent, female organs differentiate regardless of chromosomal or gonadal sex. Consideration of internal genitalia is obviously important for assessment of a patient's marriageability and chances of fertility, but is not of prime importance in assigning sex.

5. *External Genitalia*

By the 9th week of development experts can diagnose sex from external genitalia; the differences are obvious by the 12th week. Masculine genitalia form if adequate male hormone is present during the period of sexual differentiation, regardless of the type of gonads present. If no gonads are present, or no male hormone is produced, female external genitalia develop regardless of genetic sex.

The external genitalia are the criterion commonly used in sex diagnosis; this is certainly the most important criterion in the newborn. The genitals may be unreliable indicators of chromosomal or gonadal sex; often it may be extremely difficult to differentiate a female with a hypertrophied clitoris and rugose labia majora from a cryptorchid hypospadiac with a bifid scrotum.

6. *Habitus*

The development of body form is dependent on genetic and hormonal factors. If intersex patients are diagnosed early and given proper hormonal therapy, the desired appearance can usually be developed. Although changes of sex after infancy are not recommended, contradictory habitus in poorly managed cases is usually the compelling reason for patients to seek a change. Such cases were relatively common a few years ago; there is little excuse for allowing them to occur today.

7. *Sex of Rearing*

After infancy, sex of rearing becomes an exceedingly important criterion of sex. Often by the age of two the social pattern is so well established that a change could cause serious mental confusion. Money *et al.*,[18] after a psychological study of 76 intersexes, concluded that when a change of assignment was made later than early infancy, life adjustment was not significantly improved and was often made worse. Rare voluntary requests for change of sex should be given serious consideration; such a person may have become convinced, because of serious conflict between assigned sex and external genitalia, that a mistake was made at birth. In such instances, after psychiatric consultation, a change may be desirable.

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8. *Gender Role and Orientation*

Good evidence supports the view that psychological masculinity and femininity develop after birth according to experiences of growing up; once firmly established at about 18 months the conviction can rarely be successfully erased.[18] The practical value of this finding is that there need be little fear of psychological maladjustment if it seems appropriate to raise a child opposite to its chromosomal and gonadal sex. Of course development of the desired gender role and orientation in such cases depends upon good clinical management.

DEFINITION OF INTERSEXUALITY

An intersex is a person in whom there is a contradiction of one or more of the following morphological criteria of sex: chromosomal sex, gonadal sex, internal sex organs and external genitalia.

DIAGNOSIS OF INTERSEXUALITY

Most intersexes may be recognized easily at birth because of equivocal external genitalia. Intersexuality is likely to be missed if the genitals appear normal; the condition in such cases is usually detected in adolescents who show abnormal sex development.

The usual diagnostic problem is to differentiate the male pseudohermaphrodite from the female with congenital virilizing adrenal hyperplasia. This may now be done fairly easily by the chromatin test and by determination of urinary 17-ketosteroids. A positive chromatin test and elevated urinary 17-ketosteroids, that can be suppressed by cortisone, establish a diagnosis of congenital adrenogenital syndrome. Female pseudohermaphroditism with non-progressive virilization is strongly indicated if the ketosteroid excretion is normal in a chromatin-positive patient, but the rare condition of true hermaphroditism cannot be excluded unless the gonads have been examined microscopically.

A negative chromatin test in an intersex with ambiguous genitalia usually indicates male pseudohermaphroditism, though true hermaphroditism again cannot be ruled out until the gonads have been examined microscopically.

Intersexes with normal-appearing genitalia are rarely detected in infancy or childhood, unless characteristic physical signs are present or large surveys are conducted.[19] A negative chromatin test in a person with female genitalia suggests gonadal dysgenesis (Turner's syndrome and related conditions)[12] or a type of male pseudohermaphroditism (testicular feminization syndrome).[20] A diagnosis of gonadal dysgenesis is established by the presence of a high titre of urinary gonadotrophin (FSH) and characteristic skeletal defects.[12] Male pseudohermaphrodites with feminizing testes are usually detected when they present with amenorrhœa or inguinal hernia.

A positive chromatin test from a person with male genitalia suggests seminiferous tubule dysgenesis (Klinefelter's syndrome and related conditions)[21] or an excessively masculinized female pseudohermaphrodite. One characteristic feature of seminiferous tubule dysgenesis is an excessive amount of pituitary gonadotrophin (FSH) in the urine; 17-ketosteroid excretion is normal or subnormal. The rarer condition, female pseudohermaphroditism with excessive virilization would be suggested by an increased excretion of 17-ketosteroids in the urine.

POSSIBLE MEDICO-LEGAL PROBLEMS

Assignment of sex in intersexuality being based on several criteria, errors of diagnosis and of judgment may occur. Also, undue emphasis on a criterion of sex (chromosomal, gonadal or hormonal), not essential for social and psychological adjustment, may give rise to differences of opinion as to sex. Those directly concerned with problems of sex have often wondered whether medical and legal opinion would differ greatly concerning modern biological views of sex. It was this concern, sparked by curiosity, that prompted consideration of the medico-legal aspects of intersexuality. Illustrative cases will be described to raise possible questions.

Males with Criteria of Female Sex

CASE 1.—Jones and Scott[22] described a fairly normal-appearing boy who was diagnosed as a female pseudohermaphrodite with congenital excessive virilizing adrenal hyperplasia. The patient was designated a male at birth because the genitalia were predominantly masculine. Investigation five years later revealed ovaries, tubes and a uterus. The criteria of sex were as follows:

TABLE I.

Criteria of sex	*Male*	*Female*
Chromosomal sex		*
Gonadal sex		*
Sex hormone pattern	*	
Internal sex organs		*
External genitalia	*	
Habitus	*	
Assigned sex	*	
Gender role and orientation	*	

Criteria of maleness predominate because he was assigned as a boy and developed a male sex role.

This case illustrates the prime importance of external genital anatomy in sex assignment at birth. Although female internal genitalia were not suspected at birth, this knowledge probably would not have affected the designation. To adapt this boy further to the male sex, the internal genitalia and ovaries were removed. Medically there is no doubt about the appropriate sex for this patient.

CASE 2.—Money *et al.*[25] described a young married man who was a female pseudohermaphrodite with non-progressive virilization. The external genitalia were equivocal; a uterus, tubes and ovaries were present; breasts and feminine habitus had begun to develop at puberty. After removal of contradictory sex structures, plastic repair of the external genitalia and hormone therapy, the young man had married and was well adjusted. The criteria of sex, before treatment, were as follows:

TABLE II.

Criteria of sex	*Male*	*Ambiguous*	*Female*
Chromosomal sex			*
Gonadal sex			*
Sex hormone pattern			*
Internal sex organs			*
External genitalia		*	
Habitus			*
Assigned sex	*		
Gender role and orientation	*		

It is obvious that a misdiagnosis was made at birth, but at the time there was no practical way of detect-

ing chromosomal sex. In view of the ambiguous external genitalia, the error was understandable. There would be no excuse for misdiagnosis in such a case today. This case illustrates how well such patients can become adjusted in the "wrong" sex if they are properly managed. It would have been ridiculous to alter this patient's sex at puberty, as he had developed an unchangeable masculine gender role and orientation. Thus, medically this person is a male, despite outright contradiction by five criteria of sex.

CASE 3.—A patient with seminiferous-tubule dysgenesis associated with Klinefelter's syndrome was studied here recently. He had gynæcomastia, eunuchoidism, a slightly female body contour, a small penis, no beard, and a high-pitched voice. The criteria of sex were as follows:

TABLE III.

Criteria of sex	*Male*	*Ambiguous*	*Female*
Chromosomal sex			*
Gonadal sex	*		
Sex hormone pattern		*	
Internal sex organs	*		
External genitalia	*		
Habitus		*	
Assigned sex	*		
Gender role and orientation	*		

Clinically and socially this patient is a male. Although he has several feminine characteristics, he has only one morphological criterion of femaleness. Many such patients have XXY sex chromosomes, thus they are not really chromosomal females.

CASE 4.—Armstrong[26] described a male patient with transvestism, a strong desire to wear female clothing and to be accepted as a female. The patient's external genitalia were masculine; his habitus was fairly feminine, mainly because he took female hormones; his mannerisms, facial expressions and voice were feminine. All morphological criteria of sex except habitus indicated maleness, and the female habitus was produced by self-administered hormones. The patient's gender role and orientation were female.

This patient is not an intersex by our definition, as there is only contradiction between physical and psychological criteria of sex. It is this type of patient that is publicized so much; for example, "Father of Two Becomes Woman". It is well known that in Denmark selected patients are emasculinized by castration and by amputation of the penis, and then feminized by plastic construction of female-like external genitalia and hormone therapy. What is the person's sex now?

The criteria of sex in such a person would be as follows:

TABLE IV.

Criteria of sex	*Male*	*Female*
Chromosomal sex	*	
Gonadal sex	castrated	
Sex hormone pattern		hormonally created
Internal sex organs	*	
External genitalia		surgically created
Habitus		hormonally created
Assigned sex	*	
Gender role and orientation		*

Only one of the four criteria indicating femaleness developed naturally.

If such a person's sex were changed, criteria of the female would predominate. Would this make him a female? The answer is "no" clinically and probably socially also. He is a mutilated, non-marriageable eunuch who will probably not be accepted by either sex. If accepted as a female legally, embarrassing social and legal problems might ensue.

Females with Criteria of Male Sex

CASE 1.—A happily married woman studied because of tiredness and amenorrhœa had good breast development, a normal vagina and normal external genitalia.[23] Testes and vestigial female internal organs were discovered at laparotomy. The diagnosis was testicular feminizing syndrome (male pseudohermaphoditism); the criteria of sex were as follows:

TABLE V.

Criteria of sex	*Male*	*Female*
Chromosomal sex	*	
Gonadal sex	*	
Sex hormone pattern		*
Internal sex organs		*
External genitalia		*
Habitus		*
Assigned sex		*
Gender role and orientation		*

This woman is unequivocally female by clinical and social standards.

Patients with gonadal dysgenesis and chromatin-negative nuclei would show similar criteria of sex, and similarly there would be no doubt about their medical sex.

CASE 2.—Brewer, Jones and Culver[27] reported a case of true hermaphroditism that had an unusual feature. The certification of birth stated that the patient was male. However, the mother did not accept the doctor's decision and raised her baby as a girl. The infant developed into an attractive woman: breast development was good, the habitus definitely feminine. She became concerned about her genitalia when marriage was proposed: the genitals were ambiguous but more masculine than feminine. Surgical exploration revealed ovotestes, a uterus, tubes and a vagina. The criteria of sex were as follows:

TABLE VI.

Criteria of sex	*Male*	*Ambiguous*	*Female*
Chromosomal sex		*not determined*	
Gonadal sex		*	
Sex hormone pattern			*
Internal sex organs			*
External genitalia	*		
Habitus			*
Assigned sex	*		
Gender role and orientation			*

Obviously the patient is female clinically. What is her legal sex, the sex on her birth certificate or the sex the mother decided?

CASE 3.—A 15-year-old girl with male pseudohermaphroditism was described by Jones and Scott.[24] She had testes, female genitalia with a large phallus and a vagina 5 cm. long; no other female organs were found. The criteria of sex were as follows:

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TABLE VII.

Criteria of sex	*Male*	*Female*
Chromosomal sex	*	
Gonadal sex	*	
Sex hormone pattern	*	
Internal sex organs	predominantly	
External genitalia		predominantly
Habitus	predominantly	
Assigned sex		*
Gender role and orientation		*

This patient is a female clinically because of her feminine gender role and orientation, and predominantly female external genitalia.

Nowadays similar patients, known to be chromosomal males at birth, are also raised as females, as their genitalia are more suited for that sex. Reconstruction of the genitalia and removal of contradictory structures enable such persons to lead fairly normal lives as females. In the past such females were usually not suspected of having testes until they became extremely masculinized. Many tragic cases could be cited. One will illustrate the consequences.

CASE 4.—A young married woman became concerned about her masculine habitus, her sexual inadequacy, and her strong affection for members of her sex. On examination it was found that she was actually a male with perineal hypospadias. In view of the patient's masculine orientation and masculine organs, the physician recommended that she change her sex. The change of registration and annulment of marriage were carried out without legal complications.

This case illustrates that in rare instances sex should possibly be changed if satisfactory psychological adjustment may be expected. This patient could have remained a female and her role improved by castration, plastic surgery and hormone therapy. But, for reasons previously stated, it was considered best to change "her" sex. After repair of the hypospadias the patient appeared to be well adjusted.

It should be clear now that sex should not be designated by any one criterion; several should be considered. The relative value of each depends on the particular case, with regard to age, degree of psychological adjustment, surgical possibilities for reconstruction, etc. The modern trend is to make an early decision based on all available evidence: often this is a matter of clinical experience. Assignment of sex in such cases should be considered carefully, but an unequivocal decision should be made as soon as possible after birth.

Many possible questions with legal implications may be raised concerning persons in whom there is a contradiction of criteria of sex: Could such persons consummate a marriage? Would they create problems in the field of wills and inheritance? Could such persons, claiming that they were not real males or females, escape charges of rape, indecency and adultery? The answers to these and other questions will become obvious after the next section (Part II) has been read.

GENERAL PRACTICE

THE GENERAL PRACTITIONER AS A SPECIALIST

W. VICTOR JOHNSTON, M.B.*

SOME CANADIAN medical educationalists have computed that it costs about $30,000 to produce a general physician and $50,000 to produce a specialist. These figures seem to reflect the relative importance which is placed by educationalists on the preparation for medicine as practised by general physicians and specialists. Many factors have contributed to the development of this situation in medical education. We submit that the time is rapidly approaching when as much thought, planning, and resulting expense should be devoted to the training of general practitioners as to that of specialists.

With increasing rapidity there is emerging a new concept of the general practitioner trained to take a total approach to all the common problems of his patients and, what is just as important, trained to work in reciprocal cooperation with highly competent specialists.

It is becoming increasingly clear that the majority of people want a personalized type of medical care, in spite of all factors tending to depersonalize it. They want it to be warmly human as well as scientific. They want their physician to bring the best technical knowledge as well as the priceless remedy of a personal interest in them as people. They wish an emergency service at all times, as serious illness knows no convenient hours, and this requires that the doctor must be interested in making house calls.

The idea that a group of specialists can replace good general physicians has been advocated for years but there is increasing evidence that this is too expensive, cumbersome and inefficient. The myth that a general practitioner cannot perform the common tasks of medicine as well as specialists can be easily dispelled by a thorough study of good general practice conducted by well-trained general physicians and backed by a consulting group of specialists.

There is a very articulate school of medical opinion that overemphasizes to the general practitioner the increasing complexity of modern medicine. In this, they are doing a disservice to medicine, where

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every discovery should facilitate progress. Of course it is becoming more complex with the multiplying number of specialties, but from the viewpoint of the family doctor, whose duty it is to get the great bulk of sick people better, it is becoming less complex. Why? Simply because he can treat the great majority of his patients more surely and more rapidly than ever before. It is easier now to treat effectively the 85% of common ailments and promptly to get specialized help for the remaining 15%. The problem is that in order to do this he must keep abreast of modern medicine. But this obligation is not peculiar to general physicians.

The day of the "solo" general practitioner is gone, but overspecialization is not the answer. Certainly we agree that much of general practice falls short of the best standards of modern medicine, but there are also great differences in the competence of specialists, particularly when they venture into the field of general practice as many of them do. Their work leaves much to be desired when they are in general practice as, for instance, when the gynæcologist treats his patients for non-gynæcological ailments. He is not trained for this.

One of the threats to Canadian health today is a preoccupation with exaggerated problems of health, a neurotic fear of illness, iatrogenic disease and just plain overtreatment. It should be easy to prove that these dangers are more inherent in general medical care when provided by groups of specialists than by competent general physicians.

In truth, the function of the modern family doctor is much too difficult and important to be left to someone not specifically trained for the task. It sounds a little paradoxical but medicine should consider family medical practice as a specialty. An appreciation of its unique and special qualities reflects the emergence of general practice as one of the dynamic forces in medicine. The corollary is that specialists should be trained as, and consider themselves as consultants and confine their work to their specialty.

Because of its special features, good modern general practice is evolving into a specialty. Moreover, training its practitioners to give highly technical care of patients as individual members in their particular family, social and work surroundings, is becoming recognized as a difficult specialty. The cost of an efficient program for training such doctors will prove in time to be as great as that of training specialists.

CASE REPORT

MYXOMA OF THE LEFT ATRIUM*

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PRIMARY TUMOURS of the heart are rare, figures varying from 0.05%[1] to 1.05%[2] of all necropsies. Nevertheless, recent advances in the techniques of anæsthesia and cardiac surgery with the resulting possibility of cure render ante-mortem diagnosis imperative. Several excellent reviews of this subject may be found in the literature,[3-7] and no attempt will be made to duplicate these.

This paper is a report of the preoperative diagnosis and successful removal under hypothermia of a left atrial myxoma in a young child. It is believed that this is the first case embodying all these features to be reported.

D.G., an 8-year-old girl, was admitted to the Victoria General Hospital on May 12, 1959, with a history of sudden onset of weakness of the left arm and leg. Her health had been good until a few days before admission. Examination revealed motor weakness of the left arm and leg and of the left side of the face, with hyperactive reflexes, an extensor plantar response and slight sensory impairment on the left. The right pupil was slightly dilated and reacted sluggishly to light. Blood presure was 100/50 mm. Hg; the pulse rate was 90 per minute and regular. The femoral arteries were palpable; there were no murmurs or thrills.

Spinal fluid examination was negative, and skull radiographs were normal. A right carotid arteriogram suggested some degree of atrophy of the right side of the brain. An electroencephalogram revealed a slow-wave focus in the right parieto-occipital region.

The patient's condition improved rapidly in hospital and she was sent home, where she continued physiotherapy. She improved while at home until July 10, 1959, when she suddenly lost the use of both legs. Motor function was lost in both legs, and there was discolouration of the left leg up to the knee and of the right leg to the inguinal ligament. The changes in the right leg disappeared within half an hour, but the left leg remained cold, pale and completely paralyzed. There was no pulsation in the left femoral, popliteal and posterior tibial arteries. Except for a tachycardia of 112 per minute and slight residual weakness of the left arm, the remainder of the physical examination was normal. A left lumbar paravertebral block was performed without relief. From a femoral arteriogram, a filling defect was noted near the lower part of the femoral triangle.

A left femoral embolectomy was performed next day, and several fragments of grey gelatinous material with adherent blood clot were removed from the left femoral artery. Microscopic study of sections of the

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embolus revealed myxomatous tissue. The patient made an uneventful recovery except for minimal gangrene of two toes, and was transferred to the Halifax Children's Hospital for further investigation on July 15, 1959.

Urinalyses were normal on several occasions. The hæmogram on admission was: Hb. value 10.20 g. and white blood cell count 19,400 per c.mm., with 70% neutrophils, 22% lymphocytes and 8% monocytes. An electrocardiogram with œsophageal leads recorded at several levels was normal, as were results of chest radiographs and cardiac fluoroscopy.

With the knowledge derived from embolectomy, two possibilities as to the origin of the embolus were considered. It was thought possible, though doubtful, that paradoxical embolism could have taken place, i.e. the embolus could have originated in the right side of the heart or in the peripheral veins and crossed an atrial septal defect. Alternatively it could have originated in the left atrium or ventricle, probably the former. Because these investigations failed to indicate the site of origin of the embolus, it was considered that right heart catheterization and selective angiocardiography were indicated.

On August 27, these procedures were carried out. A No. 7 Cournand catheter was passed into the heart via a left antecubital vein: values for oxygen saturation and intracardiac pressure and pulse wave contours were found to be normal. The catheter could not be passed across either the atrial or the ventricular septum. These findings excluded paradoxical embolism, and selective angiocardiography was then carried out from the pulmonary artery in order to visualize the left atrium and ventricle. As can be seen in Fig. 1a, a filling defect was demonstrated in the left atrium. This was considered to be due to a myxoma.

On September 15, 1959, under hypothermia, the chest was opened by a trans-sternal incision. The venæ cavæ were occluded and the heart was allowed to empty. The left atrium was widely opened and a soft jelly-like multilobed tumour 2 x 3 x 3 cm. was found attached to the anterior atrial wall by a short pedicle which was 3 mm. in diameter. This was removed by curettage. During closure, several attacks of ventricular fibrillation ensued and were successfully treated by electrical stimulation. The patient made an uneventful recovery from her cardiac surgery and was discharged from hospital on September 26, 1959. When seen six weeks after operation, she was clinically well. At the time of writing, eight months postoperatively, the patient is free of symptoms.

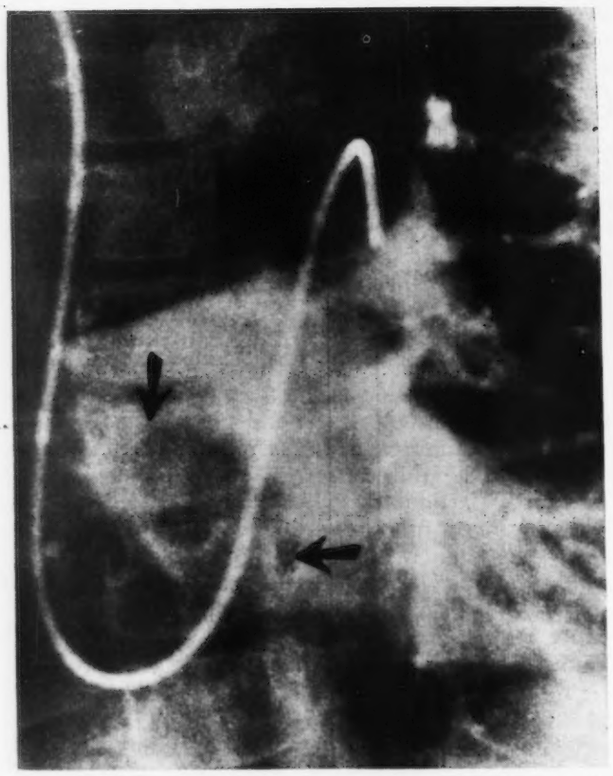

Fig. 1a.—Plate from the selective angiogram showing the filling defect in the left atrium (marked by arrows).

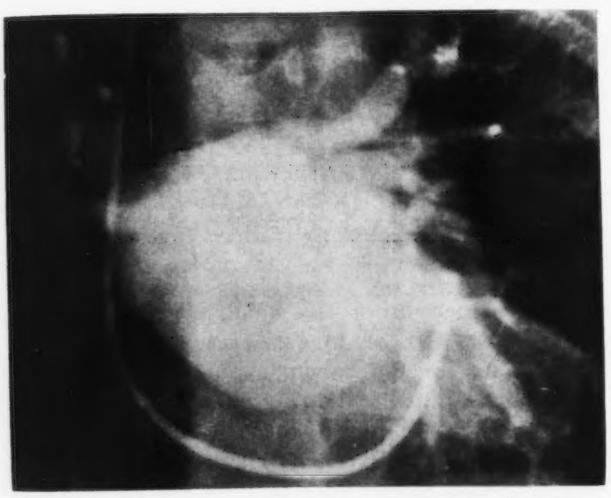

Fig. 1b.—Plate from a selective angiogram showing a normal left atrium.

DISCUSSION

Diagnosis of a left atrial myxoma in a child is most unusual. Campeau and David[7] found that, of 215 myxomas reported in the literature, only six have been described in children. This is perhaps contrary to what one would expect, since the most widely accepted theory of the origin of these tumours is that they arise from embryonic rests in the region of the fossa ovalis.[8] On the other hand, the possibility that these tumours may be present for years without causing symptoms, cannot be ruled out. The incidental finding of myxoma at necropsy has been described,[9] and the low incidence in children probably does not discredit the embryonic rest theory.

Embolism is a common and much-overlooked occurrence in myxoma of the heart. Campeau and David found that 42% of the cases reviewed by them had embolism, and at least two[10, 11] of the six children previously reported had this complication. From the consistency of the tumour, i.e. its extreme friability, this high rate is to be expected. Many bizarre and puzzling neurological (as in this case) and other syndromes may be produced by such emboli.[11, 12]

In most cases, however, the emboli have not been in accessible regions. Bland's report[11] appears to be the only previous one in which biopsy of an

embolus confirmed the diagnosis of myxoma. Although Edwards and Johnson[14] report a case in which embolectomy revealed myxomatous tissue, the patient died before the site of origin of the embolus could be demonstrated. The recognition of myxomatous tissue is not difficult, even in the gross, as was noted in our case.

Angiocardiography is the only uniformly successful procedure by which the diagnosis may be made. Of the 18 instances of successful removal of an intra-atrial myxoma previously reported, in only nine had the diagnosis been established preoperatively; and of these, seven were diagnosed by angiocardiography.[6] In all these cases, the filling defect was clearly defined, as it was in our patient. Confusion may arise, however, particularly in cases of mitral stenosis with atrial fibrillation, in which thrombus may accumulate in the atrium and produce a similar shadow.

Bigelow, Dolan and Campbell[13] reported the first successful surgical removal of a myxoma under hypothermia. Since then, this technique has been successfully used in nine patients,[6] including the present one.

In all except one of the other cases, extracorporeal circulation was used. The choice between hypothermia and cardio-pulmonary bypass appears to be an individual one. However, the removal of a left atrial myxoma under hypothermia always involves the risk of embolism. For this reason, the use of the pump-oxygenator with elective cardiac arrest may be preferable. Hypothermia, however, is a safer procedure, and the use of this technique as illustrated by this case and others has demonstrated its feasibility.

SUMMARY

A case of left atrial myxoma in an 8-year-old child is reported. The diagnosis was made after embolectomy by selective angiocardiography. The tumour was successfully removed under hypothermia. It is believed that this is the first case embodying all these features to be reported.

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SHORT COMMUNICATIONS

A METHOD FOR THE HISTOLOGICAL EXAMINATION OF BONE MARROW GRANULES

W. B. LEACH, M.D., M.Sc.,* *Vancouver, B.C.*

THE HISTOLOGICAL examination of bone marrow is a useful and sometimes essential adjunct to the regular aspiration procedure. Such an examination usually entails, however, a surgical biopsy undertaken by an orthopædic surgeon under general anæsthesia from sites such as the sternum and iliac crests. Procedures for the histological examination of material obtained by sternal puncture are generally tedious, exacting and difficult to perform, if satisfactory preparations are to be obtained. That of Cappell, Hutchison and Smith,[1] though giving excellent results, has these disadvantages.

The method to be outlined below has recently been established in this laboratory and is proving to be a fairly simple, easy method of obtaining histological preparations of the granules obtained during bone marrow aspiration. It is, in many instances, supplying useful additional information over and above the routine bone marrow morphology.

MATERIALS AND METHODS

1. *The usual equipment employed in the obtaining of bone marrow aspirations.* In this laboratory it is customary to use a Turkel trephine needle to obtain the aspirate, which should consist of 2-3 ml., the first portion being used to make the routine hæmatological smears and squash preparations. The remainder is placed in a small tube containing sequestrene or other anticoagulant. A minimum of 2-3 ml. of material should be obtained. A good granule content is essential for a satisfactory histological preparation.

2. *Lengths of glass tubing with an internal diameter of approximately 6-7 mm., cut with square ends to a length of about 8 cm.* This size has been found to be convenient because the ends can be plugged with small rubber vaccine-bottle stoppers (Fig. 1).

3. *A standard small centrifuge.*

4. *Bouin's fixative.*

5. *A supply of pasteur pipettes and 10 ml. syringes with 21 gauge needles, test tube rack and applicator sticks.*

As much sternal marrow aspirate as possible is transferred from the sequestrene tube to a 6-mm. glass tube, one end of which has been closed by a vaccine-bottle stopper. Two tubes may be used if required. Care should be taken to make sure that as many granules as possible are transferred to the tube. The open end of the tube is then also

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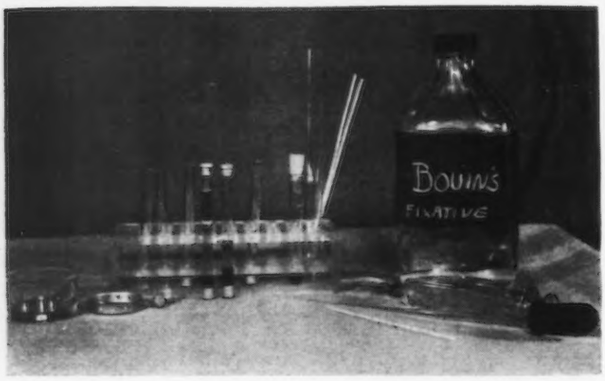

Fig. 1.—Equipment currently in use.

stoppered and the material centrifuged at low speed, for approximately three to five minutes. At this time examination of the tube will reveal that the aspirate is divided into three layers. Red blood cells are observed at the base of the tube, plasma in the central area and a zone of marrow granules at the surface (Fig. 2). This zone should be 1-2 mm. in thickness, depending on the granule content of the specimen. The surface of the centrifuged specimen is then overlaid carefully with Bouin's fixative and placed in a rack for a period of several hours, or until the aggregate of marrow granules is coagulated into a relatively firm mass. At this time, with the use of a 10-ml. syringe and a fine needle the red blood cells and serum can be conveniently drawn from the base of the tube through the vaccine-bottle stopper. This is facilitated if the granule plug is gently loosened on the sides of the centrifuge tube by means of a sharp needle, fine scalpel blade or a sharpened applicator stick. As the plasma and red blood cells are then withdrawn into the syringe, the plug with its overlaying Bouin's fluid will follow the extraction down to the base of the tube. Bouin's solution is then forced in through the needle so that the aggregated bone marrow granules are surrounded on all sides by fresh Bouin's fixative. The tube remains in this state for a further period of 12 hours, at which time the bone marrow block is gently extracted from it and will be found to be of sufficient consistency to be run through the routine histological dehydration systems employed by most laboratories.

The resulting sections may be stained in a manner preferred by the individual. The stain usually employed in this laboratory is the hæmatoxylin-eosin and occasionally the Unna-Pappenheim methyl green pyronine method for D.N.A. and R.N.A.

DISCUSSION

The method described above for the preparation of bone marrow granules by histological methods is readily adaptable to any laboratory which has the equipment to undertake sternal marrow examinations and routine histological preparations. The only difficulties which have been encountered in this laboratory so far involve:

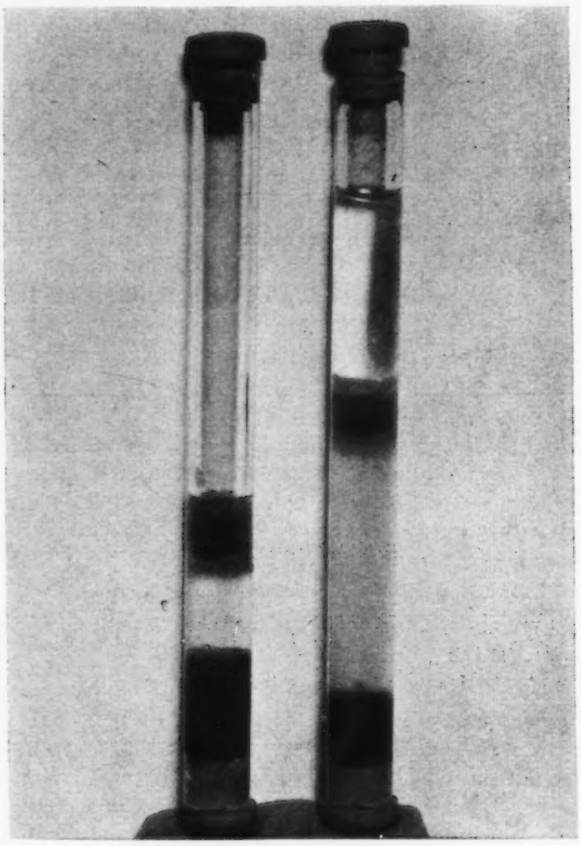

Fig. 2.—Tubes during preparation of granule blocks. The right tube shows the block overlaid with fixative.

1. Insufficient numbers of granules in the specimen in which the aggregate of granules obtained is 1 mm. or less in thickness and therefore is liable to some fragmentation during the handling of the specimen.

2. Occasionally, the granules will be found at the base of the marrow column instead of the surface. If this occurs, specimens may still be obtained by

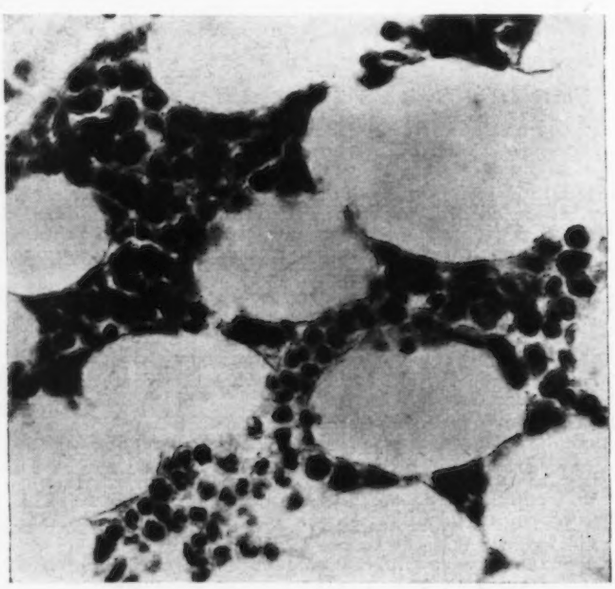

Fig. 3.—Bone marrow section showing plasma cell aggregations. H. & E.

removing the superficial serum and cells with a pipette and overlaying with Bouin's fixative.

The accompanying photographs illustrate the type of sample which has been obtained. Fig. 3 illustrates a case of multiple myeloma in which clumps of plasma cells may be easily identified. Fig. 4 illustrates a case of anaplastic sarcoma of lymphoid tissue, Hodgkin's sarcoma type, in which masses of sarcoma cells can be clearly identified among the marrow granules. The usefulness of the method is well illustrated in this case in that the bone marrow morphology from the hæmatology department did not clearly identify the disease process.

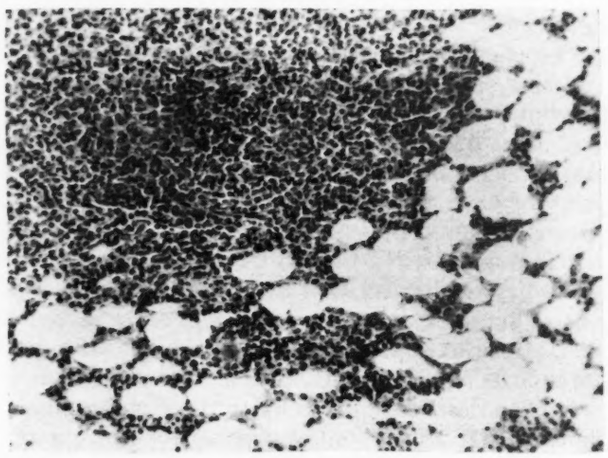

Fig. 4.—Anaplastic sarcoma of lymphoid tissue (Hodgkin's sarcoma type) replacing cells. H. & E.

Further application of this method for use with fluorescent staining procedures has been recently under study. With absolute ethyl alcohol as a fixative, it has been found that very satisfactory sections can be obtained which lend themselves to ultraviolet light examination after staining with the various fluorescent materials, in particular acridine orange.[2, 3]

SUMMARY

A method for the histological examination of bone marrow granules obtained during routine bone marrow aspiration is described. This method of examination is considered a useful adjunct to the more routine hæmatological examination of the bone marrow. The method is adaptable to any department capable of carrying out bone marrow aspirations and histological procedures.

I wish to express my thanks to Dr. J. W. Thomas and his staff of the Department of Hæmatology, for the marrow aspirates, and to Dr. P. S. Vassar and Mr. C. F. A. Culling for their assistance in the fluorescent technique.

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THE FIRST RECOGNITION OF CUMARIN

A correspondent has sent us the following account of the first recognition of cumarin by Frank W. Schofield, D.V.Sc.—ED.

DURING THE winter of 1921-22, numerous outbreaks of a hitherto unrecognized disease in cattle were reported to the Ontario Veterinary College at Guelph. The affected animals suffered from massive hæmorrhages which were rapidly fatal in almost 80% of cases. Many young animals died from exsanguinating hæmorrhage after de-horning.

Frank W. Schofield, D.V.Sc., was, at that time, lecturer in pathology and bacteriology at the College. He undertook a detailed investigation of 11 herds of afflicted animals reported from scattered points in southern Ontario, and he reported his findings to a meeting of the American Veterinary Association held in Montreal in August 1923. His paper was published in the Journal of that Association in February 1924[1] under the title "Damaged sweet clover: the cause of a new disease in cattle simulating hæmorrhagic septicæmia and blackleg".

He found that the winter fodder of the herds struck down by the "bleeding" disease invariably contained mouldy sweet clover, and he therefore attributed the blood dyscrasia of these animals to some poisonous substance in the clover. Sweet clover had previously been listed among poisonous plants by L. H. Pammel;[2] and Schofield, quoting from this author's "Manual of Poisonous Plants", stated that "the sweet clovers contain the substance cumarin ($C_9H_6O_2$) which is found in the Tonka bean, sweet vernal grass, vanilla grass, etc."

After Schofield's report, this substance "cumarin" was isolated from sweet clover by chemists and was later synthesized as "cumarol", a powerful anticoagulant. It was first used commercially under the name "warfarin" as a rat poison. It is now universally used in medicine as dicoumarol.

The pioneer work of Dr. Frank Schofield in 1922 at the Ontario Veterinary College laid the foundation for the development of dicoumarol and other related anticoagulant drugs.

Early in his career, Dr. Schofield spent three and a half years in Korea, teaching at Severance Medical College under the Presbyterian Church in Canada. On retiring from the Ontario Veterinary College, he received a pressing invitation to return to Korea. He is now giving his services voluntarily to the College of Veterinary Medicine and continuing his primary interest of presenting the Christian faith to students in the National University of Seoul.

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GUANETHIDINE IN THE TREATMENT OF HYPERTENSION

THE QUEST for effective antihypertensive drugs has become so intense that evaluation of one such agent is scarcely in progress before it is superseded by another or several others of reputed superiority. Specificity of pharmacological action, and consistency and dependability of clinical effects are qualities which are required of such drugs before they can be considered to possess practical therapeutic value. In addition to these requirements they should be fully absorbed in a predictable time after oral administration, should have minimal or no undesirable side effects and should induce no significant tolerance after repeated administration. Recently two new and promising drugs have been introduced which induce a blood-pressure-lowering effect by their specific action on the sympathetic nervous system without the distressing side effects associated with the ganglion-blocking agents. These drugs, bretylium tosylate (Darenthin) and guanethidine sulphate (Ismelin), are similar in their pharmacological properties but possess important clinical differences. The former has been disappointing from the clinical point of view because its action is irregular and its administration is associated with a high incidence of tolerance. Guanethidine, on the other hand, appears to hold distinct promise as a potent antihypertensive agent of potential therapeutic value. Indeed its apparent attractions are so great that they have caused a flurry of studies of the pharmacological and therapeutic action of this drug on an international scale. In witness thereof the July 9, 1960 issue of *Deutsche medizinische Wochenschrift* is devoted almost entirely to papers reporting evaluations of guanethidine in many centres of Europe, the United Kingdom and America, and the three leading "original articles" in the August 20, 1960 issue of the *Lancet* consist of reports of its intensive investigation and therapeutic assessment. In Canada, the earliest and most comprehensive studies on guanethidine have been contributed by Dr. Jacques Genest and his co-workers in the Clinical Research Department of the Hôtel-Dieu Hospital, Montreal. The results of the investigations of this group are published elsewhere in this issue.

Pharmacological studies on dogs have revealed the marked and prolonged blood-pressure-lowering action of guanethidine on renal and neurogenic hypertension, as well as its blocking effect on the hypertension induced by amphetamine, ephedrine and the carotid occlusion reflex. The mode of action of this drug is not entirely understood but it is believed to interfere over a prolonged period of time with the release and/or distribution of the neurohumoral transmitter at the sympathetic neuromuscular junction (noradrenaline). It does not produce any parasympathetic blockade.

The consistent, sustained, and at times profound lowering of blood pressure in hypertensive humans to whom this drug has been administered on a long-term basis is now adequately confirmed. It also reduces the normally anticipated rise in blood pressure after physical exercise when given intramuscularly or intravenously in doses of 20 to 40 mg. to normotensive individuals.

Cardiac catheterization studies have been reported as showing an appreciable drop in peripheral resistance following guanethidine administration. Its effects on circulatory hæmodynamics have been described as similar to those of ganglion-blocking agents but the latter are not as well tolerated and do not produce as profound a hypotensive action. No consistent change in cardiac output at rest or after exercise was noted following single intravenous doses of 20 or 40 mg.

Studies of the effects of long-term administration on renal function of hypertensive patients revealed no demonstrable change in glomerular filtration rate. Lowering of the effective renal plasma flow paralleled the degree of reduction of the elevated blood pressure. These patients also exhibited marked reduction in excretion of sodium ions and water, and a lesser degree of reduction in potassium ion excretion. Serum sodium, potassium and urea nitrogen levels showed no significant change in most patients on long-term guanethidine therapy. In normal humans the intravenous administration of a single dose of guanethidine was associated with reduction of urinary excretion and of inulin and para-aminohippuric clearance, which was believed to be due to increased resistance in renal afferent arterioles. This renal vasoconstriction was most pronounced 30 minutes after injection of guanethidine but persisted for at least 90 minutes or longer.

Intravenous administration in some patients results in a transient acute hypertensive effect, which is considered by some to contraindicate the intravenous use of guanethidine for patients with severe or malignant hypertension, with possible phæochromocytoma, with obvious organic vascular disease or with left ventricular failure. On the other

hand, others consider the intravenous administration of guanethidine is justified when prompt reduction of blood pressure is urgently required, as in the case of patients with malignant hypertension accompanied by acute pulmonary œdema. In such cases, however, subcutaneous pentolinium may be preferable since its action is more easily controlled and of shorter duration.

After 20 mg. or 40 mg. doses of guanethidine intravenously, the pulmonary ventilation was consistently increased and the oxygen uptake rose in three of five patients studied. The mean resting pulmonary wedge and pulmonary arterial pressures were relatively unchanged but the calculated pulmonary vascular resistance showed a slight decrease which was maintained during exercise. It is to be noted, however, that these studies were carried out with subjects in the recumbent position only.

Preliminary studies with C^{14}-labelled guanethidine indicated that the amount excreted in the urine 24 hours after an intravenous dose was approximately 50%, and after an oral dose, only about 20%. By 72 hours after an intravenous dose, urinary excretion had risen to 72%, compared with 36% of the oral dose excreted in the same period. The slow excretion after oral administration probably accounts for the prolonged and cumulative action of this drug. During the 72 hours after oral doses, approximately 20 to 25% of the drug was excreted in the stool, whereas only 3% of intravenously administered guanethidine was excreted in the stool of one patient in the three days after injection. Specimens of bile in a patient who had a T-tube inserted following cholecystectomy failed to show more than trace amounts of C^{14}-labelled guanethidine after an intravenous dose. In animal experiments, concentration of the drug in various body tissues was mainly intracellular and was highest in the kidney.

Side effects reported to date have included orthostatic and exercise hypotension with faintness, giddiness and weakness, diarrhœa, bradycardia, morning fatigue, mental depression, parotid tenderness, nasal obstruction, tremor, fluid retention and congestive heart failure, breathlessness, failure of ejaculation, priapism, and the development of acute peptic ulceration. In the majority of instances these undesirable effects have been trivial or minimal in degree and readily controlled by symptomatic therapy.

To date there has been no indication that patients on prolonged guanethidine therapy have developed tolerance to this drug, necessitating increasingly larger doses to sustain its hypotensive effect.

In the clinical application of this drug, most observers recommend its combination with one of the other antihypertensive agents, particularly with hydralazine or reserpine, and with a diuretic agent which stimulates sodium excretion, such as chlorothiazide or hydrochlorothiazide. Opinion regarding the efficacy of such combined therapy is not unanimous, however.

In the usual oral daily dosage range of 30 mg. to 120 mg., guanethidine is generally considered to be a safe, potent and consistently effective drug of considerable value in the treatment of arterial hypertension of essential or malignant types, or that secondary to renal disease, phæochromocytoma and a variety of other causes.

INTESTINAL MALABSORPTION

THE causes of intestinal malabsorption are varied and the list of conditions in which it is found is still probably far from complete. This syndrome provides a common meeting ground for workers in a number of different specialties, as mentioned by Kay[1] in his paper on malabsorption, of special interest to surgeons. Although easily diagnosed when present in its fully developed form, malabsorption can often go undetected, especially in adults. Ruffin and Tyor[2] emphasize that most patients who have impaired fat absorption will have grossly normal stools and, if diarrhœa is present, it may resemble that seen in patients with irritable bowel. The inevitable result of malabsorption is weight loss and it will be almost always found, although it may not be mentioned by the patient. Green and Wollaeger[3] report that weakness and lassitude were the chief complaints in 95% of their 124 patients with sprue. Diarrhœa was present in 73% and a minimum of 10 lb. of weight loss was almost universal but was never the chief complaint. Abdominal complaints were common but were usually mild in nature.

The introduction of absorption tests of radioactively tagged lipids has provided a simple and relatively inexpensive method of demonstrating steatorrhœa and decreased fat absorption. Radioactivity of the stools collected over 48 to 72 hours and of blood samples collected four, five and six hours after ingestion of the test meal containing radioactive iodine tagged triolein is determined, and absence or presence of malabsorption is quickly established. Using oleic acid instead of triolein in a second test, it is possible to distinguish the steatorrhœas of impaired absorption from those due to a defect of digestion. The latter group includes diseases of the pancreas, of the liver and biliary system. Ruffin and Tyor[2] state that 50% of patients who had undergone subtotal gastrectomy (Billroth II) or a gastroenterostomy with or without vagotomy will have steatorrhœa. Widespread application of the absorption tests is apparently uncovering some degree of malabsorption in an even higher proportion of cases after gastric surgery and in many other conditions which are of interest not only to the gastroenterologist.

One condition that may become more frequently recognized is mucoviscidosis. This disease, once known to pædiatricians as fibrocystic disease of the pancreas, is reported to be quite common in adults. Recent editorials[4, 5] containing excellent summaries of this disorder indicate the great interest in this condition. Koch,[6] who has carried out electrolyte determinations of body sweat on

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relatives of patients with mucoviscidosis, found among them a high incidence of peptic ulcer, frequent pneumonias, cor pulmonale and insufficiency of digestion. Unexplained cachexia or dehydration with low blood pressure and tendency to circulatory collapse was often encountered. Emphysema with onset early in life and associated with peripheral cyanosis and clubbed fingers was part of the picture. Mendeloff[7] reported abnormalities of sweat in five out of 24 and abnormalities of duodenal juice in four out of 24 patients with obstructive emphysema. Eight of 25 patients with cylindrical bronchiectasis showed abnormal concentrations of sweat electrolytes. He stresses that full-blown fibrocystic disease involves the pancreas, the lung, the liver (focal biliary fibrosis which may develop rapidly to a generalized mixed form of cirrhosis with portal hypertension) and the salivary and sweat glands. A comparison of sweat chlorides and intestinal fat absorption was carried out by Wood and his co-workers[8] in chronic obstructive emphysema and fibrocystic disease of the pancreas. Peterson[9] makes a plea that the sweat test be applied to adults with endobronchial disease. Absorption test studies may explain the loss of weight seen in many patients with long-standing pulmonary disease, commonly diagnosed as emphysema.

Organic disease of the small bowel, such as regional ileitis and diffuse infiltration by neoplasm, is a well-known cause of malabsorption. One of the lesser known causes of malabsorption is acute enteritis as is illustrated by two cases reported by King and Joske.[10] Awareness of the temporary nature of the disturbance may prevent unnecessary interference if a history of recent enteritis can be elicited.

Although only a few years old, aspiration biopsy of the small bowel has become very popular. Several methods are now available, as was demonstrated at the recent meeting of the American Gastroenterological Association (New Orleans, April 1-2, 1960).

The most recent report by Fone *et al.*[11] on jejunal biopsies in 58 patients with the clinical diagnosis of adult sprue disclosed that the typical histological picture was present in only 27 cases. A second group of 27 patients had abnormal jejunal mucosa which differed markedly from that seen in sprue and some of these patients improved on B_{12} and others on folic acid administration. A third group of four cases showed normal jejunal mucosa and they responded to parenteral iron, which relieved their abdominal symptoms.

The striking symptomatic improvement of sprue achieved with gluten-free diets and the possibility of successfully treating many other causes of malabsorption make it imperative that diagnostic facilities for their recognition be much more widely available than at present. There is no reason why radioactive iodine tagged lipid absorption tests could not be carried out in any laboratory where iodine uptake tests are performed. W.G.

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TO BUFFER OR NOT TO BUFFER

TELEVISION commercials frequently display the agonized facies of a model simulating unbearable pain. Following the ingestion of the advertised proprietary medicine the look of agony is immediately wiped out and replaced by a radiant smile before the medication could have passed the cardia. Such prompt relief of agony attests to the value of acetylsalicylic acid which is the important ingredient in most proprietary pain relievers.

The value of acetylsalicylic acid as a pain reliever is without question. Its ability to cause gastritis, and even gastric erosion with bleeding, is also well proven, particularly if taken on an empty stomach with little or no fluid to dissolve and distribute it within the gastric lumen.

Because of the irritating effect of particles of acetylsalicylic acid upon the gastric mucosa it has become popular to combine the acid with an antacid or buffer. The claim has been made that such a combination increases the rate of absorption of the drug. There are conflicting reports in the literature as to the worth of such a combination. A recent study by Levy and Hayes[1] is illuminating. They carefully investigated eight widely known brands of acetylsalicylic acid tablets. They found a very wide variation between these brands as to the time of dissolution of the tablets and the time of absorption of the drug. Some plain acetylsalicylic tablets dissolved and were absorbed more rapidly than some buffered products. Their investigation also indicated that the small amount of buffering substance employed had no evident effect either within the stomach or in the rate of absorption.

Acetylsalicylic acid is a very valuable drug in the relief of a great many of the minor pains and discomforts which beset modern mankind (and especially womankind). It should never be taken as a whole tablet on an empty stomach without plenty of fluid. It is best administered as a fine powder in a capsule with ample fluid which will distribute it well over the gastric mucosa, leading to rapid absorption. This is the best method of restoring a look of peaceful serenity to the facies of the suffering, and the gastric mucosa will remain serene during the process. Of course, acetylsalicylic acid tablets can be well divided by chewing them thoroughly. While this would protect the gastric mucosa and increase the rate of absorption of the drug, the taste would cause some minor agony of its own. N.S.S.

REFERENCE

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FAVISM

THE report by Gower and Frommer[1] of London, England, of a case of favism in a Cypriot child reminds one that this condition may not be as rare as is commonly thought, even in Canada. The child was admitted to hospital with a history of rapidly increasing pallor and the passage of dark-red urine for 24 hours. He complained of pain in the neck and had vomited several times. The clinical diagnosis was that of acute hæmolytic anæmia, and recovery followed transfusions and administration of cortisone for six days. On discharge, the hæmoglobin level was 87%, but six months later it had dropped to 60%, although the child did not show obvious abnormality. Eight months after the first admission, he was readmitted with sore throat and again with a history of passing dark-red urine for 24 hours. It was then discovered that he had eaten broad beans, which had been purchased frozen, on the day before the onset of hæmoglobinuria. The diagnosis of favism was apparent.

Although the red cells appeared normal, it was possible to demonstrate that they behaved abnormally after incubation with acetylphenylhydrazine, a test used for the detection of "primaquine-sensitive" red cells. This test was devised by Beutler *et al.*[2] and reveals the presence of a familial abnormality of red blood cells. In this condition, the red cells are deficient in glucose-6-phosphate dehydrogenase, a deficiency which is also the basis of some unusual drug sensitivities which cause hæmolysis.

Favism has been known for centuries to affect persons originating from the Mediterranean area and has been prevalent on the island of Sardinia as well as in Sicily and in southern Italy. Szeinberg *et al.*[3] recently reported studies of erythrocytes in patients with favism and with drug-induced acute hæmolytic anæmia and Szeinberg *et al.*[4] also reported a selective occurrence of this abnormality in some Jewish groups. A country-wide screening in Israel has established that about 10% of the non-Ashkenazic Jews and 5% of the Arabs and Druzes are carriers of this potentially hæmolytic trait. Szeinberg *et al.*[5] point out that in view of the fact that these population groups represent about 50% of all the inhabitants of Israel it is rather surprising that relatively few cases of hæmolytic reactions follow administration of drugs. They cite work by Dern and associates who investigated drug-induced hæmolysis in subjects with "primaquine-sensitive" red cells. Transfusion of "defective" erythrocytes labelled with Cr^{51} from six subjects into normal recipients who were given 3.6 g. of sulphanilamide daily produced marked hæmolysis of these cells in all six cases. A similar sensitivity was demonstrated after ingestion of N-4 acetylsulphanilamide and sulphacetamide but not after ingestion of sulphadiazine, sulphamerazine or sulphathiazole. Szeinberg *et al.* found that three patients with this enzymatic abnormality developed acute hæmolysis on the third or fourth day of sulphapyridine administration. In one of their sensitive subjects the reaction was very severe and began with gross hæmoglobinuria. They had also observed acute hæmolytic anæmia which developed two to three days after administration of sulphadiazine in five men and two women. Six of these individuals were Iraqi Jews and one a Yemenite. In all, subsequent examination confirmed the presence of an enzymatic defect in their erythrocytes. It appears therefore that various sulphonamides act differently as far as hæmolytic activity in these patients is concerned. The reason for this is at present unknown although Szeinberg *et al.* believe that it could be determined by the structure of the side chains of the drug molecule or the metabolites formed in the body.

An editorial in the same issue of the *Lancet* which reported the case of favism refers to the need for consideration of favism in the differential diagnosis of unexplained attacks of hæmolysis and hæmoglobinuria. In Canada, with the recent influx of large numbers of people of Mediterranean origin, it is important to keep this condition in mind for several reasons. Favism is a distinct possibility, as broad beans are probably available in packaged form all year round and the condition would not therefore be necessarily seasonal. The presence of large numbers of people with this erythrocyte enzyme deficiency may bring forth other, hitherto unknown hæmolytic anæmias due to inhalation of pollen of spring flowers or other plants and, which is perhaps even more important, due to ingestion of drugs.

With the Beutler test at hand for detecting the abnormal red cells, we need not go to the length of precipitating an attack by ingestion of broad beans. Inability of the abnormal cells to retain glutathione in the presence of a reducing agent is the basis of another test.

The significance of the sensitivity to some sulphonamide derivatives assumes particular importance when one remembers that some hypoglycæmic drugs used in diabetes in ever increasing amounts and diuretics like chlorothiazide are all sulpha derivatives. As diabetes is prevalent among both Jews and Italians, the relatively high incidence of this sensitivity due to enzyme deficiency of erythrocytes should be kept in mind. W.G.

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LETTERS TO THE EDITOR

MORE ABOUT PSYCHOANALYSIS

To the Editor:

In a recent issue you printed a letter from Dr. D. J. B. Makins (*Canad. M. A. J.* 83: 392, 1960) applauding the earlier short note by Dr. I. Schiffer on the psychological meanings and trauma surrounding physical procedures. The letter was entitled "In Praise of Psychoanalysis". I would like to dissent.

All would agree that tact is necessary in hospitals; most have seen patients and others derive unusual pleasure or displeasure when exposures occur or instruments, hands or fingers investigate some areas of the body. From this basis your two writers elaborate confidently with statements that have had a currency of 40-50 years without anyone's proving their reality. Any real psychiatric study before an emergency or even an elective laparotomy is not only impossible because of the time and place available but is thereby made irrelevant. This is compounded by the not unlikely concurrence of a sick mind and a sick abdomen, which should make the operation wholly inevitable.

Dr. Schiffer's opinion, and it is, like mine, only an opinion, is shared by few psychiatrists in Canada or England, though (without necessarily adding to its dignity) it might be occasionally acceptable in a few coastal cities in the States. As I have studied preoperative patients in a psychiatric milieu for 2 research years (for any time period necessary) it seems to me that his notions are gross exaggerations of transient events in suggestible people where the questioning, listening and meaning are strongly biased. Were I an "anal erotic" with rectal carcinoma I would prefer to have the cancer discovered than pay the apparently enormous price of bringing into some sort of awareness whichever anal phase dominated.

It is marginally appropriate to praise psychoanalysis as presented by any two physicians in the last 20 years. Psychoanalysis and its theory made its psychiatric contribution—not an enormous one, but not a minute one—decades ago, and it may still have a certain fashion in conservative Canada. However, there is no literature whatsoever that proves with discernment the position assumed by these writers. Support can only be anecdotal or unproven generalization, both characteristics of a body of theory that has routinely avoided, if not fled from scientific confirmation. These confident and wholly subjective ideas are not proved either by the sincerity or strength of their statement; the reverse is usually so. If we were to agree with them because of the expressed certainty, the world would still be flat.

WM. MITCHELL, M.D.,
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To the Editor:

With reference to Dr. I. Schiffer's paper in a previous issue of this Journal (82: 132, 1960), this writer wishes to comment upon the letter pertaining to the above article, as written recently by Dr. Makins in the August 20, 1960, issue.

It is extremely gratifying to hear that a fellow practitioner holds psychiatry and particularly psychoanalysis in such high regard and that he feels these particular branches of medicine can accomplish such great things as the elimination of neurotic complexes in medical students so that they will be better practitioners and better able to deal with their patients.

It is well to be aware of the fact that, whereas a few particular individual patients can benefit greatly from psychoanalysis or long-term psychotherapy, the great majority are refractory to such treatment for one reason or another, such as their level of intelligence, the nature of their illness, their inclination and motivation, and so on. Unfortunately, psychotherapeutic treatment and psychoanalysis will not accomplish for every patient what many indivduals seem to think they will do. With a few particular patients much can be brought about in the way of personality change and improved adjustments. However, with the great majority of patients the best one can hope for is symptomatic benefit through supportive attitudes.

I hope Dr. Makins does not mean what he says when he states that he hopes all presurgical patients will have a preoperative psychoanalysis. A routine psychoanalysis cannot be brought about as readily as this, and of course a full psychoanalysis is something which runs into many years. It may be that he is thinking of a psychiatric assessment, or possibly psychological appraisal. There is merit for such, particularly when the operation is elective and it is questionable as to the basic motivation behind the patient and how the patient might react to the surgery if it is unsuccessful.

It is difficult to conceive of preoperative assessment in every patient, particularly when a patient is suffering from an acute surgical disorder which demands immediate attention. Also, it is unlikely that there will ever be enough staff available to assess and engage in treatment all would-be medical students. It is also questionable whether this might not be treated as a big joke by the bulk of the clientele involved, and it is doubtful that many young persons would benefit greatly from such "treatment".

So far as the effect of numerous surgical and physical procedures on patients in examination is concerned, there is no question that these are often provocative measures and are extremely disturbing and upsetting to many patients. Be this as it may, when such procedures must be carried out psychological implications are of secondary importance. They must be considered and all must be done by way of making a patient as comfortable as possible. Certainly the *attitude* of the individual doctor at the time plays considerable importance.

Dr. Makins might well be referred to a paper which appeared many years ago in this Journal, from which I think he would glean much as far as the reality situation in psychiatry today is concerned. I refer to a paper by Dr. Elliott Emanuel[1] entitled "Has Psychiatry Been Oversold?"

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11010 Jasper Avenue.,
Edmonton, Alta.

REFERENCE

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Medical News in brief

COMPARISON OF ISONIAZID-CYCLOSERINE WITH ISONIAZID-PAS IN THE THERAPY OF CAVITARY PULMONARY TUBERCULOSIS

The data from a large co-operative study of the clinical effectiveness of the two drugs cycloserine and isoniazid used together were analyzed and the efficacy of this regimen was measured against that of isoniazid and para-aminosalicyclic acid (PAS) given concurrently to a control group of patients with cavitary tuberculosis in 14 cooperating hospitals.

In several respects, results in the isoniazid-cycloserine-treated group tended to show that this regimen is less efficacious than isoniazid-PAS. Storey (*Am. Rev. Respiratory Dis.*, 81: 868, 1960) reports the results as: A higher incidence of roentgenographical evidence of progression of the disease—7% as compared with an incidence of 2% among the control group; a much higher incidence of clinical failure to respond satisfactorily to treatment, which necessitated change in drug regimen in 12% of the cases as compared with 2% in the isoniazid-PAS-treated group; a lesser incidence of cavity closure; a lower incidence of appearance of bacteriological "conversion" of the bronchopulmonary secretions; and a more rapid emergence of bacterial resistance to isoniazid with a greater overall incidence of resistance to isoniazid.

Although (in general) well tolerated, the regimen is not without its own toxicity as evidenced by the occurrence of one convulsive seizure, one instance of optic neuritis, three hypersensitivity reactions, and perhaps 13 instances of mental aberration or behavioural change. In the isoniazid-PAS group, there were nine hypersensitivity reactions, including one death from acute yellow atrophy. The great bulk of PAS toxicity was associated with gastro-intestinal irritation.

SIGNIFICANCE OF LATERAL AND GENERALIZED RETINAL SHEEN

Generalized retinal sheen is a wet, glistening appearance of the entire retina, including the nasal field, which is frequently associated with toxæmia of pregnancy and with glomerulonephritis. It is seldom seen in the normal population. It is almost always associated with retinal arterial spasm, which helps greatly in differentiating it from *lateral* retinal sheen. Its prompt decrease or disappearance following diuretic therapy suggests that it represents retinal œdema.

Lateral sheen is a wet, shiny appearance of the lateral portion of the retina seen in normal persons under 40 years of age. This glistening appearance is more intense around the macula. Although it frequently extends just beyond the mid-line, its medial extent is seldom more than one disc diameter. The younger the patient, the more intense and greater its area of distribution. Although wet in appearance, lateral sheen probably does *not* represent retinal œdema, since it is not influenced by diuretic therapy. It probably represents the anterior limiting membrane of the retina.—W. D. Finnerty, Jr. *et al.*: *Ann. Int. Med.*, 52: 819, 1960.

SERUM GLUTAMIC OXALACETIC TRANSAMINASE (SGO-T) IN CONGESTIVE HEART FAILURE

The SGO-T level was found to be frequently elevated, often markedly, in patients with acute congestive failure or acute exacerbations of chronic congestive failure. This fact applies to cases of right, left or combined congestive failure. The highest SGO-T values were found in patients with chronic lung disease with secondary right heart failure.

This elevation may be correlated with other abnormal results from liver function tests and the pathological findings of centrilobular atrophy and necrosis. The rapidity of onset of the failure is an important factor. This is further substantiated by the absence of SGO-T elevation in an out-patient group. In these patients the degree of failure was static and of long standing. In addition, marked elevation of SGO-T has been demonstrated in patients with rapid arrhythmias resulting in the sudden onset of acute hepatic congestion. Liver damage, with concomitant SGO-T elevation, is even more likely to occur in chronic lung disease with cardiac decompensation and pulmonary insufficiency, since both anoxia and passive congestion are present. This was clearly demonstrated in this study by Fragge, Kopel and Iglauer (*Ann. Int. Med.*, 52: 1042, 1960) and in previous studies.

There is need for a clinicopathological study of patients with acute pulmonary œdema and elevated transaminase levels, without clinical or electrocardiographical evidence of acute myocardial infarction. This is necessary to define more clearly the significance of SGO-T elevation in this condition, and the role of congestion in its production.

EFFECT OF PARENTERAL VITAMIN B_{12} ON MUSCLE CONTRACTION IN HYPOTHYROIDISM

Administration of 1 mg. vitamin B_{12} to 73 euthyroid and 10 hyperthyroid patients caused no change in the Achilles reflex contraction time; 29 untreated hypothyroid patients and seven inadequately treated hypothyroid patients showed abrupt, transient prolongation of the Achilles reflex contraction time of greater than 40 milliseconds after parenteral administration of 1 mg. vitamin B_{12}. Twelve hypothyroid patients who were overtreated with thyroid had an abrupt shortening of their reflex contraction time of 20 milliseconds or more after administration of vitamin B_{12}. Eight of the patients had previously shown prolongation at the time therapy was initiated.

Lawson and Weissbein (*Am. J. M. Sc.*, 239: 77, 1960) conclude that vitamin B_{12} has some unknown effect on the contractile process of skeletal muscle in patients who are hyperthyroid and who are under- or over-treated with exogenous thyroid. These patterns of muscular response after administration of vitamin B_{12} have proved pragmatically useful in the hands of the writers when indecision as to the adequacy or inadequacy of thyroid dosage, or a problem in the diagnosis of hypothyroidism, has arisen.

(Continued on advertising page 23)

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POSTGRADUATE COURSES

THE FOLLOWING POSTGRADUATE MEDICAL REFRESHER COURSES, SPONSORED BY CANADIAN UNIVERSITIES, ARE SCHEDULED FOR THE PERIOD SEPTEMBER 4, 1960—MARCH 7, 1961.

Title of course	*Location*	*Starting date*	*Ending date*	*Fee*	*Apply to*
Clinically Applied Basic Sciences	Halifax, N.S.	September 4 (once weekly,	April 26 30 sessions)	$5.50	The Director, Post-Graduate Division, Faculty of Medicine, Dalhousie University, Halifax, N.S.
Medicine, Chest Diseases	Jubilee Auditorium, Edmonton, Alta.	October 17	October 18	$25.00	Secretary, Alberta Division, C.M.A. and/or Dept. of Medicine, University of Alberta
Refresher Course in Anæsthesia	Dept. of Anæsthesia, University of Toronto	October 17	October 21	$50.00	Division of Post-Graduate Medical Education, University of Toronto
Arthritis	Sunnybrook Hospital, Toronto, Ont.	October 27	October 27	$15.00	Division of Post-Graduate Medical Education, University of Toronto
Surgical Aspects of Common Diseases	Dept. of Surgery, Toronto General Hospital	November 7	November 9	$35.00	Division of Post-Graduate Medical Education, University of Toronto
Dalhousie Refresher Course	Halifax, N.S.	November 7	November 10	$10.00	The Director, Post-Graduate Division, Faculty of Medicine, Dalhousie University, Halifax, N.S.
Surgery—The Management of Surgical Problems in Infancy and Childhood	Jubilee Auditorium, Edmonton, Alta.	November 21	November 22	$25.00	Dept. of Surgery, University of Alberta, and/or Secretary, Alberta Division, C.M.A.
Clinical Pædiatrics for General Practitioners	Department of Pædiatrics Hospital for Sick Children Toronto, Ont.	November 24	November 25	$25.00	Division of Post-Graduate Medical Education, University of Toronto
Pædiatrics	B-Lecture Hall, Faculty of Medicine Bldg., Vancouver General Hospital	November 23	November 25	$25.00	Committee on Post-Graduate Education, Medical Administration Office, Vancouver General Hospital
Anæsthesiology	" "	January 25	January 27	$25.00	
Surgery } one day	" "	February 13	February 15	$25.00 ea.	
Medicine } overlap		February 15	February 17	($40.00 both)	
Psychiatry	Halifax, N.S.	January 30	February 1	$15.00	The Director, Post-Graduate Division, Faculty of Medicine, Dalhousie University, Halifax, N.S.
Annual Refresher Course in Public Health and Preventive Medicine	School of Hygiene, University of Toronto	February 6	February 8	$35.00	Division of Post-Graduate Medical Education, University of Toronto
Obstetrics and Gynæcology	Jubilee Auditorium, Edmonton, Alta.	March 6	March 7	$25.00	Secretary, Alberta Division, C.M.A., 501 Alexandra Bldg., Edmonton, Alberta
Regional Courses consisting of a coordinated series of six weekly meetings deal with selected subjects in medicine, surgery, obstetrics, pædiatrics, and two specialty fields, the specific topics being chosen by the local hospital staff or district Medical Society program committee working with the Director of the Post-Graduate Division. These courses are held in from six to eight centres in the four Atlantic Provinces each year.					The Director, Post-Graduate Division, Faculty of Medicine, Dalhousie University, Halifax, N.S.

PUBLIC HEALTH

SUMMARY OF REPORTED CASES OF NOTIFIABLE DISEASES IN CANADA*
ISSUED BY THE PUBLIC HEALTH SECTION, DOMINION BUREAU OF STATISTICS

Disease	Week ended (1960): July 23	July 30	Aug. 6	Aug. 13	Cumulative total since beginning of year: 1960	1959
Brucellosis (Undulant fever) (044)	10	8	5	5	77	68
Diarrhœa of the newborn, epidemic (764)	1	—	1	1	34	54
Diphtheria (055)	—	1	—	—	21	17
Dysentery:						
(a) Amœbic (046)	—	—	—	1	2	2
(b) Bacillary (045)	37	40	29	22	1,554	504
(c) Other and unspecified (047, 048)	8	9	12	39	259	76
Encephalitis, infectious (082.0)	—	2	1	8	22	11
Food poisoning:						
(a) Staphylococcus intoxication (049.0)	9	—	—	—	309	6
(b) Salmonella with food as vehicle of infection (042.1)	49	15	27	8	550	334
(c) Unspecified (049.2)	—	—	2	—	19	49
Hepatitis, infectious (including serum hepatitis) (092, N998.5)	42	56	66	64	3,347	3,179
Meningitis, viral or aseptic (080.2, 082.1)	109	20	34	40	318	170
Meningococcal infections (057)	3	2	1	2	107	132
Pemphigus neonatorum (Impetigo of the newborn) (766)	—	—	—	—	7	2
Pertussis (Whooping cough) (056)	62	72	91	56	3,602	3,546
Poliomyelitis, paralytic (080.0, 080.1)	15	21	28	30	288	520
Scarlet fever and Streptococcal sore throat (050, 051)	158	157	98	137	16,293	15,590
Tuberculosis:						
(a) Pulmonary (001, 002)	106	104	50	48	2,879	3,055
(b) Other and unspecified (003-019)	7	8	5	3	348	314
Typhoid and Paratyphoid fever (040, 041)	13	5	—	1	197	454
Venereal diseases:						
(a) Gonorrhœa (030-035)	301	347	303	298	9,252	8,664
(b) Syphilis (020-029)	30	31	32	40	1,201	1,305
(c) Other† (036-039)	—	—	—	—	3	3

*Figures for the Yukon are received four-weekly and are, therefore, shown in the cumulative totals only.
†Including chancroid, granuloma inguinale and lymphogranuloma venereum.

ABSTRACTS *from current literature*

MEDICINE

Variable Responses of Hyperlipæmic Patients to Altered Food Patterns.

H. B. BROWN AND I. H. PAGE: *J. A. M. A.*, 173: 248, 1960.

Studies of 51 patients are presented illustrating three distinct types of hyperlipæmia. In addition to hyperglyceridæmia (the triglyceride fraction showed the greatest degree of elevation) and hypercholesterolæmia, both widely recognized types, a third form, mixed hyperlipæmia, was observed. Dietary treatment was effective in its influence on hyperglyceridæmia and in mixed hyperlipæmia, and relatively less effective in hypercholesterolæmia.

In this study the serum lipid fractions were calculated from determined values of total lipid, total cholesterol, free cholesterol, and phospholipid phosphorus. Triglycerides were calculated as the difference between the total lipid content and the sum of free cholesterol, cholesterol esters and phospholipid. Of the 51 patients with elevated serum cholesterol levels, 40 were between the ages of 35 and 60 and eleven were between 20 and 34 years. Hyperlipæmia was the only evidence of abnormality in 15 patients while the other 36 presented with manifestations of some form of atherosclerosis.

Thirty-four patients were given a low-fat and vegetable-oil diet in succession for many months.

In nine hyperglyceridæmic patients, nearly normal levels of all serum lipids were achieved with the low-fat diet pattern, but the triglyceride level remained relatively high. On the vegetable-oil diet cholesterol levels were not only lowered but also much more stable. Two hyperglyceridæmic patients showed higher serum cholesterol levels with the vegetable-oil than with the low-fat diet. Either food pattern reduced serum lipid levels in 15 hypercholesterolæmic patients; they did not, however, reach normal values in all cases. Ten patients with mixed hyperlipæmia responded to both diets, with serum lipids dropping readily and remaining at normal levels.

W. GROBIN

Neuritis Occurring After Insect Stings.

N. P. GOLDSTEIN, C. W. RUCKER AND H. W. WOLTMAN: *J. A. M. A.*, 173: 1272, 1960.

Although allergic reactions to the stings of bees and wasps have been recorded in numerous instances, such manifestations have usually been exaggerations of the common local response, urticaria or an anaphylactic type of reaction. Several "near fatal" allergic reactions to bee or wasp stings have been reported. Less common is the development of neuritis after the sting of an insect although this type of reaction has been recognized for over 20 years at least. Petechiæ may be found in the central nervous system when the reaction to the sting of an insect is fatal, and cerebral œdema, intraventricular hæmorrhage, and meningeal hyperæmia have also been described in such cases.

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Presumably such changes may involve cranial or peripheral nerves with the production of neuritis though histological evidence of such involvement is lacking. The authors provide a detailed description of the history and findings of three patients who developed neuritis after the sting of a bee, a hornet, and a spider respectively. None of the patients was considered to be of an "allergic disposition". In one instance, papill-œdema occurred; in the second patient, neuritis involved one upper extremity; and in the third, there was evidence of neuritis of the first and second divisions of the trigeminal nerve. In each case the involved nerve was in proximity to the location of the insect sting. It was postulated that these were examples of "allergic neuritis" of a nature similar to that of delayed serum reactions following antitoxin administration. In two of the three patients the reaction abated spontaneously over a period of time.

Serum Insulin in a Case of Severe Diabetes Mellitus showing Remission.

K. W. TAYLOR: *Brit. M. J.*, 1: 1853, 1959.

Serum insulin studies were carried out in a patient who experienced spontaneous remission from severe diabetic ketosis after a period of several months' treatment with moderate doses of insulin. A glucose tolerance test a year later showed that the diabetes remained quiescent. On studying the effect of the patient's serum on the glucose uptake of isolated rat diaphragm *in vitro*, it was found that there was apparently no insulin available during ketosis but that there was insulin in the serum during remission. By removing insulin antagonists through fractionation of the serum it was possible to show that insulin was present in the serum obtained from the patient during ketosis. These results are considered to support the view that circulating insulin antagonists play a role in diabetic ketosis. The author suggests that the insulin antagonist may be pituitary-dependent and that growth hormone may be in some way connected with human diabetes. W. GROBIN

Lengthy Diabetes: Causes and Effects.

W. R. ROGERS AND B. HOLCOMB: *A.M.A. Arch. Int. Med.*, 105: 746, 1960.

Among 12,000 medical records of diabetic patients seen in 35 years of private practice by one of the authors, there were 126 whose diabetes had been present for 25 years or more. Of these, 114 had records which were adequate for study and analysis. Comparison of these 114 patients with the total group of diabetic patients revealed certain significant differences. The median age at onset of diabetes was 33 years in those with "prolonged" diabetes as compared to 50 years in the total diabetic group. Forty per cent of the former had exhibited obesity as compared with 77% of the adults in the total group. Seventy per cent of those with prolonged diabetes had complications. Among the patients without complications there was a significantly lower incidence of glycosuria and ketonuria. Obesity also was less frequent in the uncomplicated cases than in those with complications.

The authors believed that in general the longevity in these diabetics with lengthy survival was due to careful control of the metabolic disorder, to the development of diabetes at a younger than average age, and to a more favourable heredity. Of the 30% who had no diabetic complications, nearly all had survived while of those with complications one-half had died. Death was due to cardiovascular-renal complications in 82% and none died from diabetic coma, cancer or infection. W. GROBIN

Changes in Serum Proteins and White Blood Cells in Hepatitis.

H. H. VON MÄRKI AND A. WICK: *Schweiz. med. Wchnschr.*, 90: 657, 1960.

The behaviour of white blood cells and serum proteins was investigated by differential counts and electrophoretic serum protein examinations in 127 hospital cases of hepatitis, between 1955 and 1959.

Although epidemic hepatitis is accompanied by necrotic processes in liver tissue comparable to those involving the myocardium in cases of myocardial infarction, the expected increase of alpha-globulins and of neutrophile granulocytes did not occur; there was instead a monocytosis and increase in the gamma globulin fraction of the serum proteins. The authors believe that this particular behaviour is largely due to the effect of the reticulo-endothelial system in the liver, but they could not exclude the influence of the parenchyma. In these patients with hepatitis the mechanism of suppression of the alpha globulin reaction, usually associated with inflammatory conditions, is unknown. There was a parallelism between the increase of monocytes and the degree of elevation of the gamma globulins, according to these authors. However, the rapid initial increase in monocytes was followed by a much more rapid return to normal, whereas the changes in serum proteins were much slower in developing and in returning to normal. This suggests that the latter is a more reliable diagnostic aid. W. GROBIN

Optic and Peripheral Neuritis—Probable Effect of Prolonged Chloramphenicol Therapy.

J. T. JOY, R. SCALETTAR AND D. B. SODEE: *J. A. M. A.*, 173: 1731, 1960.

The authors report the occurrence of severe optic and peripheral neuritis in a patient who had been treated with 3 g. chloramphenicol daily for a systemic infection by *Pseudomonas pseudomallei* (melioidosis). The duration of such treatment was approximately three months before the onset of symptoms of neuritis. One year after treatment with chloramphenicol was discontinued, minimal paræsthesias in the feet after prolonged marching, small bilateral scotomas and slight enlargement of blind spots were the sole residua. Subjective visual sensation and objective neurological findings otherwise had returned to normal. Five additional cases of definite involvement of the optic nerve, associated in three instances with peripheral neuritis attributed to chloramphenicol toxicity, were also described. It was suggested that these toxic manifestations were related both to large doses of the drug and to prolonged administration. The range of total doses was 190 g. to over 1600 g. Toxic symptoms appeared as early as 42 days and as late as 22 months after the start of treatment. It was concluded that large doses of chloramphenicol for prolonged periods appeared to have a neurotoxic effect, particularly on the optic nerve, which if unrecognized or untreated could result in permanent blindness. Prompt withdrawal of the antibiotic and administration of large doses of vitamins especially of the vitamin B group were recommended in such cases.

SURGERY

The Results and Causes of Failure Following Cervico-Thoracic Sympathectomy.

D. TOVI: *Acta chir. scandinav.*, 119: 8, 1960.

This study is based on 214 cervico-thoracic sympathectomies in 148 patients with Raynaud's disease and allied neurovascular or sudomotor disturbances of the upper extremities.

The author describes the anterior approach of Leriche and Fontaine (1933), the dorsal approach of Adson and Brown (1929), the anterior preganglionic approach of Telford (1935), and the dorsal preganglionic approach of Smithwick (1939). Palumbo's chest approach is not described. Intraspinal rhizotomy (Smithwick, 1940) is mentioned.

In the present series, the anterior approach was used routinely and a preganglionic sympathicotomy was carried out consisting of division of the sympathetic trunk below the second thoracic ganglion and section of all communicating rami to the second and third ganglia. Postganglionic sympathectomy was performed on 32 upper extremities in 25 patients. This consisted of section of the sympathetic trunk below the second thoracic ganglion with resection of the stellate ganglion and all communicating rami.

Gradual deterioration occurred frequently within 6 to 12 months after a previously successful clinical result. The cause of late recurrence is believed to be incomplete denervation of the sympathetic fibres of the brachial plexus rather than regeneration of nerve fibres or hypersensitivity of denervated smooth muscle to circulating adrenalin. It is suggested that resection of the sympathetic chain from below the third thoracic ganglion up to and including the stellate ganglion, combined with intraspinal section of the anterior roots of the first, second and third thoracic nerves, will probably yield better results and decrease the number of late recurrences. Horner's syndrome is not an important contraindication, especially if the operation is bilateral, since the eye on both sides will then be similar in appearance. T. A. MCLENNAN

Islet Cell Tumours and Peptic Ulcers.

W. C. MACKENZIE AND S. T. NORVELL: *J. Roy. Coll. Surgeons Edinburgh*, 5: 191, 1960.

In 1955 Zollinger and Ellison reported the association of peptic ulceration of the jejunum with adenoma of the pancreatic islets of Langerhans. Over 100 additional reports of similar cases have been recorded since and this combination of lesions has become recognized as an entity called, by general consent, the Zollinger-Ellison syndrome. The major clinical presenting feature is that of fulminating ulceration of the upper gastrointestinal tract. The ulcers, if primary, may be in an atypical location, or if recurrent, may be stomal in position and are invariably associated with gastric hypersecretion and hyperacidity. The ulceration coexists with one or more adenomas of the pancreatic islets, usually not of the beta cell type, but often malignant and not uncommonly metastasizing. Most patients have been in the fourth and fifth decades of life; the sex incidence has been approximately equal; patients are not usually hypoglycæmic but there are some exceptions. The severe and recurring ulcer diathesis is often fulminating and frequently fatal.

Less than half the ulcers reported have been in the first part of the duodenum. The remainder were in the stomach, second and third parts of the duodenum, upper jejunum and œsophagus. Most of the associated tumours of the islets of Langerhans have been in the body and tail of the pancreas though it has been reported that about 10% were in aberrant situations. They are malignant in at least one-third of cases but the malignancy is often of low grade. Even if not malignant, multiple adenomas may be present. In summarizing the role of the islet cell tumour in this syndrome the authors note that the limited experience at hand does not warrant the conclusion that the tumour itself is directly responsible for the gastric hypersecretion or the peptic ulcer. There is no convincing experimental evidence that the pancreas produces any internal secretion related to gastric secretory activity, nor do any of the known islet cell hormones seem to play a significant part in promoting peptic ulceration. The authors state further that there is as yet no evidence that any extrapancreatic endocrine lesion is involved. It is possible that all the abnormalities in this syndrome result from an as yet unsuspected cause and the ultimate determinant of the syndrome may well have a constitutional or genetic basis.

As far as management is concerned, awareness of the lesion is a prerequisite. The pancreas should probably be explored whenever the abdomen is opened for the treatment of peptic ulcer, particularly if the patient is female, if the ulcer diathesis is severe, if the ulcer is in atypical location, if there are multiple ulcers, or if the ulcer is stomal. When one or more islet cell tumours are found in the pancreas in association with peptic ulcer, they should be resected unless the patient is a poor risk. While the main objective is resection of a neoplasm, in some cases this favourably affects the ulcer tendency as well. The ulcer itself should be dealt with by very radical gastrectomy and vagotomy.

The authors report three additional cases of this syndrome.

Cortisone in Experimental Acute Pancreatic Lesions.

S. E. BERGENTZ AND Y. EDLUND: *Acta chir. scandinav.*, 119: 24, 1960.

Cortisone has been used in treatment of human pancreatitis as it is thought to exert an anti-inflammatory effect by reducing increased vascular permeability. Pancreatitis was induced in 99 rats by ligature of the common excretory duct of the pancreas and liver, and injection of sodium taurocholate and physiological saline into the duct system of the pancreas. Cortisone had no influence on the pancreatitis produced in these animals. T. A. MCLENNAN

Gallbladder Duplication. Case Report and Review of the Literature.

C. H. RYRBERG: *Acta chir. scandinav.*, 119: 36, 1960.

The author describes one case of double gallbladder and two of cyst formation. An excellent review of the pertinent literature is given with a colour photograph of the author's specimen. The author states that when gallbladder duplication occurs, the two gallbladders usually lie in close approximation to each other, and even when true duplication is present, are enclosed in a common serosal sheath. The anomaly is then usually not detected until the gallbladder has been opened or the surgeon finds two lumens in the cystic duct. The indications for surgery are the same as for those presented by a normal gallbladder, if the duplication has been demonstrated roentgenographically.

T. A. MCLENNAN

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OBITUARIES

ALAN BROWN, M.D., F.A.A.P., F.A.C.P., F.R.C.P.[C], F.R.C.P.(Lond.), died at the Toronto General Hospital on September 7, 1960, in his 75th year. Born in Toronto in 1885, he graduated in medicine at the University of Toronto in 1909. Postgraduate training at the Babies Hospital, New York, in Germany and the United Kingdom preceded his return in 1914 to Toronto, where he took the unprecedented step of confining his practice to the care of infants and children. He gained an appointment on the medical staff of the Hospital for Sick Children and became physician-in-chief in 1919. There followed a period of 32 years until his retirement in 1951 from that appointment and from the Professorship of Pædiatrics at the University of Toronto, which can with some justification be called the Golden Age of pædiatric training in this country. An outstanding, if dogmatic, teacher; a militant crusader for better milk, better food, and the control of the communicable diseases; a stimulator of research and investigation; an author of textbooks and papers; a fund-raiser and builder; an outspoken critic of sloth and indifference to preventive procedures, Alan Brown lived an eventful life. He combined all these professional, public and administrative duties with the private practice of his profession and that of a consultant who was in great demand.

Dr. Brown's professional lifetime spanned the period of greatest progress in the reduction of infant mortality and morbidity. He would have been the last to claim a causal relationship but it is a fact that he, more than any other individual physician in Canada, contributed to the improvements which we enjoy. His other lasting claim to fame resides in his contribution to the advancement of his specialty and to the training of pædiatric teachers, investigators and practitioners.

Endowed with a vision, a persistence and an aggressiveness which is granted to few of us, Alan Brown pursued his worthy objectives with single-minded devotion and with slight regard for obstacles, human or material. His career was one of substantial accomplishment and the profession is the poorer for the loss of one of its characters and one of its most brilliant members.

Our sympathy is extended to Mrs. Brown and their two daughters.

DR. ALAN BROWN

AN APPRECIATION

The death of Dr. Alan Brown marks the end of an era in Canadian pædiatrics just as the death of Dr. A. D. Blackader signified the termination of the period which preceded it.

The dominant figure of Alan Brown occupied the centre of the stage during the period of 32 years when he was physician-in-chief at the Hospital for Sick Children. His influence on pædiatric teaching and practice was astonishing and few individuals have influenced the health of the nation as he did. He was a tireless worker and his boundless energy and ambition often drove him beyond his physical capacity. A perfectionist and a stickler for detail, he exerted an ascendancy over his associates and juniors which had to be experienced to be understood. Dogmatic, caustic, overbearing and controversial are adjectives which have been accurately applied to this great man, but these characteristics fail to do credit to the wisdom and vision which made it possible for him to ride roughshod over the day-to-day complications in pursuit of his long-term objective of better health for all children. These prickly facets of a man who chose to fight his way over inertia and opposition also take no account of the basic kindness which made him the friend of mothers and children and the greatly respected chief of doctors who learned pædiatrics the hard way under his tutelage. Generations of students will recall with gratitude that he equipped them with the definite means of handling the pædiatric problems which they would encounter, and many of them learned with surprise years later that there were other views and other methods.

Alan Brown was naturally one of the leaders in the formation of the national society of pædiatricians, the Canadian Society for the Study of Diseases of Children, now the Canadian Pædiatric Society. It was interesting to the writer as a young man to see three key figures in the organization—Dr. Alton Goldbloom of Montreal, Dr. Douglas Arnold of Buffalo, and Dr. Brown. They had few points of similarity except a common and consuming interest in the advancement of pædiatric knowledge and the identification of pædiatrics as a specialty in medicine.

In his life's work at the Hospital for Sick Children, Alan Brown was particularly close to two other colleagues, the late Dr. F. F. Tisdall and Dr. T. G. H. Drake who died only last year. The personal qualities of each of the triumvirate supplemented the others and as a team they accomplished a great deal.

The prestige and authority of Alan Brown was well earned and on occasion it was used with telling effect. For many years a crusader for the pasteurization of milk, he finally lost his patience with the hesitant legislative efforts to accomplish this basic reform. With characteristic directness he invited or commanded the presence of the Premier of Ontario at the Hospital where he showed him many patients suffering from bovine tuberculosis of bones and joints. The required legislation was passed and human infection with bovine tuberculosis was eliminated.

The honour of Senior Membership in the Canadian Medical Association was conferred on Dr. Alan Brown this year. He was not well enough to attend the function at which it was awarded but communications which were exchanged indicated clearly that he appreciated the tribute of his colleagues.

Many professional honours and awards were conferred during his lifetime. All of them were richly deserved by this good doctor and staunch crusader. He occupied a unique place in the medical life of this country; we who knew him were the better for the experience, and those to whom Alan Brown was only a legendary figure will join in mourning his passing.

A.D.K.

DR. JACOB L. COHEN, aged 59, died on September 2 at his home in Windsor, Ont. Born in London, England, Dr. Cohen graduated from the University of Toronto in 1923. He practised in Michigan for five years and since then in Windsor.

Surviving are his widow and two sons, Dr. Allan Cohen with the U.S.A.F. in Spain and Dr. Carl Cohen who is interning at Mount Carmel Hospital, Detroit.

DR. ROMAN BOHDAN LYSHAK, aged 37, died in August in Edmonton, Alta. Born in the West Ukraine, he studied at the University of Lwiw and graduated from medical school at Bonn, Germany, in 1949 when he came to Canada. He served in the R.C.A. at Fort Resolution, N.W.T., for two years, returned to Edmonton for postgraduate studies and later practised at Fort Smith. For the past three years he was on the staff of the Charles Camsell Indian Hospital.

Surviving are his widow, one son and two daughters.

DR. JOHN SURMAN SMIT, aged 56, died August 19 at Montreal General Hospital. Born in Montreal, he graduated from McGill University in 1932.

Dr. Smit had served as medical officer of health for Westmount and as consulting surgeon of the McGill Athletic Board. At the time of his death he was medical officer, eastern area, of the Bell Telephone Company of Canada. During World War II, Dr. Smit served overseas with the Canadian Army.

Surviving are his widow and two daughters.

DR. CHARLES G. SMITH, aged 65, retired Montreal anæsthetist, died August 4 at his home in L'Orignal, Ont.

Born in L'Orignal, he graduated from the University of Montreal in 1921 and studied anæsthesia in New York City before returning to practise in Montreal.

Surviving are his widow, one son and two daughters. A second son, Dr. Jacques Smith of St. Jerome, a well-known orthopædist, predeceased his father four months ago.

PROVINCIAL NEWS

BRITISH COLUMBIA

Dr. R. J. Slater, President of the Canadian Society for Clinical Investigation, has announced that Dr. Roland Wm. Lauener of Vancouver has been awarded the Schering Medical Research Fellowship for 1960.

The fellowship, which is sponsored by Schering Corporation Ltd., is awarded annually by the Society to support the research efforts of one of its members. This year's recipient will be working in the department of medicine, University of British Columbia, on assay methods of thyroid stimulating hormone, a project presently being investigated under the direction of Dr. H. W. McIntosh.

A graduate in medicine from the University of British Columbia, Dr. Lauener did his internship at the Hamilton General Hospital in Hamilton and the Westminster Hospital, London, Ont. In 1959 he was awarded a fellowship in cardiology and worked under Dr. John A. Osborne, assistant director of the Heart Station, Vancouver General Hospital.

A native of Trail, B.C., Dr. Lauener is married and lives in Vancouver.

SASKATCHEWAN

The Advisory Planning Committee on Medical Care set up by the Provincial Government has announced recently that it will receive letters, written briefs or submissions between October 1 and December 31, 1960. Public or private oral presentations of testimony on the briefs or submission which are received by the Committee will be held after November 1, 1960.

Mayor Buckwold of Saskatoon has announced that as a possible gift to the University of Saskatchewan's Golden Jubilee Fund, the City of Saskatoon is discussing with university officials the joint construction of a large auditorium. At the present time it is felt that such a building could be available for the use of Saskatoon citizens as well as for University functions.

G. W. PEACOCK

MANITOBA

The fiftieth anniversary of Manitoba Sanatorium at Ninette was celebrated on Sunday, September 11. Ex-patients, former staff members, members of the Manitoba Sanatorium Board and friends of the institution were present to honour the sanatorium and its first superintendent, Dr. D. A. Stewart, "Stewart of Manitoba" as he is known internationally.

ROSS MITCHELL

More than 10,000 social allowance recipients in Manitoba became eligible July 1 to free medical, dental, and optical care, essential prescribed drugs, and other essential medical treatment under an arrangement set up by the Government of Manitoba.

The program will cover: all elderly persons, including the infirm, who since February 1 have qualified for cash allowances in addition to their pensions; social allowance cases, who formerly received mothers' allowances; children who are wards of the province; and social allowance cases who formerly received assistance in unorganized territory.

This includes all the groups which came under sections of the new Social Allowances Act proclaimed earlier this year.

Some 10,000 people will likely be covered by the plan immediately, and the number is expected to grow to 20,000 by next March as more applications are received.

Under the plan the government will provide card holders and their families with:

Prepaid coverage for home and office calls of the doctor of their choice through Manitoba Medical Service. The doctors will provide medical or surgical care in hospitals at no charge to either the patients or the government.

Prepaid coverage for essential dental service including extraction, filling, and dentures. The dentists will pay operating costs of the plan.

Government-paid optical services, including the provision of glasses. The optometrists will bill the government for only the wholesale cost of glasses plus a small fee for services.

Government-paid essential drugs when prescribed by a doctor. Pharmacists will provide the drugs at a discount.

The government has instructed doctors to prescribe the drugs under their generic names rather than by trade names.

The Medicare cards will be sent out to those eligible on application to the provincial welfare department. —TCMP Newsletter.

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BOOK REVIEWS

HOSPITAL EVACUATION PLANNING. Emergency Health Services, Department of National Health and Welfare, Ottawa, Canada, 1960. 46 pp. Illust.

This brochure is a sequel to "A Hospital Evacuation Plan" published in 1958. Both are relevant to the "Hospital Disaster Plan" which all hospitals are encouraged to develop.

The first brochure indicates the feasibility of an emergency evacuation of a hospital and its contents; whilst the second brochure goes into more meticulous details to implement its accomplishment. Both are predicated upon the assumption that sufficient time would be available before disaster strikes.

While the limited casualties from local disasters can usually be absorbed by dispersal throughout a city's hospitals, plans must be made for casualties in much larger numbers: or even for the total evacuation of a hospital as occurred in Winnipeg when the flood encompassed hospitals and rendered them useless for occupancy.

Disaster planning was based upon the concept of nuclear warfare and the necessity for total evacuation of a target city's population, including the hospital population. Such evacuation was also predicated upon several days of diplomatic manœuvering leading up to war. In this intercontinental and submarine-launched-missile era the "time margin" philosophy has diminished; but in the event that it is not entirely obsolete, we could be considered negligent if preparation were not made to make use of whatever time does become available for evacuation.

While all doctors and nurses should be acquainted with these brochures so that they may be cognizant of the philosophy contained therein, it is imperative that hospital administrators and their hospital staff should read them in order to appraise their own state of readiness to meet extreme situations whether from warfare or other calamities.

When one reads in the brochure that about 35% of a hospital's patients could be discharged almost instantaneously to their own resources in the event of a large-scale emergency, the thought arises as to what percentage of these patients could have been discharged yesterday, or last week, to make way for the long lists already awaiting a hospital bed. Is not this condition an "emergency" of sorts?

YOUR BASEMENT FALLOUT SHELTER. Blueprint for Survival No. 1. Emergency Health Services, Department of National Health and Welfare, Ottawa, 1960, 35 pp. Illust.

This is the plan and specifications for the amateur "carpenter-stonemason" who may wish to install such a shelter in his house as just one more precautionary measure to offer some protection against the radioactive dust formed by the explosion of a nuclear or atomic weapon.

In the Prime Minister's foreword, it is noted that he does not advocate the shelter as a "cure-all" in nuclear warfare, but as "good protection against the more widespread radiation danger". It is well to accept this conservative view, as owing to the publicity given all Federal pronouncements, there is a tendency to exaggerate the value of a new approach to a frustrating problem. This applies to the discovery of a new drug.

The first four pages of this brochure are of considerable value inasmuch as they deal philosophically with the whole concept of "fall-out" and point out that shelters of any kind are merely shelters and are not a security against blast or fire. If one is far enough away from ground zero, an umbrella would shed the dusty fall-out in that area; but between the extremes of "ground zero" and the "umbrella area", there would be vast numbers who would benefit from a substantial shelter—and who knows where his location would be should a nuclear bomb descend?

SYMPATHECTOMY: An Anatomical and Physiological Study with Clinical Applications. P. A. E. Monro. 290 pp. Illust. Oxford University Press, Toronto, 1959. $11.25.

This well-bound book of 290 pages is chiefly a scholarly and stimulating report on long-term follow-up (5 years) on post-sympathectomy patients. Recording of the pattern of sweating activity has been the major tool used in assessing what has actually been accomplished by any technique of sympathectomy. The discussion of the lumbar intermediate sympathetic ganglia is of particular note and helps to explain the retention of some anatomic activity in an area after sympathectomy. Some attempt is made to correlate the anatomic and physiological findings with clinical procedures. It is for example the author's viewpoint that the retropleural approach for a thoraco-lumbar sympathectomy is physiologically more sound and leads to more permanent results than a transpleural approach. He is also of the opinion that the results of the operation in cases of hypertension have been better than generally thought and he believes this operation should be not too lightly discarded.

This book will be of particular interest to anatomists and physiologists, and to surgeons who operate upon the sympathetic system.

THE DIABETIC ABC: A Practical Book for Patients and Nurses. R. D. Lawrence. 82 pp. 12th ed. H. K. Lewis & Co. Ltd., London, 1960. $0.75 (approx.)

This is an excellent book, simply written and clearly describing the various aspects of the disease and its management. It should be most useful to nurses and to diabetics who have at least high-school education. On the other hand, the average diabetic population of an out-patient department has, in this reviewer's experience, not the necessary education to comprehend and utilize the contents of this book.

The particularly interesting method of "line ration diet" and the examples thereof are apparently working out very well in the hands of the author and, no doubt, also in England generally. However, whether this would work equally well in Canada is open to question. The preface by Dr. Lawrence to the twelfth edition indicates that few changes have been made with the exception of the introduction of information regarding oral hypoglycæmic drugs.

The stress on the British Diabetic Association, its convalescent homes, homes and holiday camps for children, old people's homes and the work of the Association in supporting research are worthy of note, as is Dr. Lawrence's appeal to all diabetics to join the Association.

All in all, this is a good introduction to diabetes and it is to be hoped that diabetics will be able to take advantage of the information contained in this volume.

MEDICAL RESEARCH AND THE DEATH PENALTY. J. Kevorkian. 75 pp. Illust. Vantage Press, Inc., New York, 1960. $2.50.

The essence of this book lies in the author's assertion: "There is need today for direct medical experimentation upon living humans, no matter how distasteful the idea may sound; as important secrets of human physiology cannot be discovered in any other way." He proposes that such need be met by offering to criminals, convicted and sentenced to execution, the alternative of "anesthetic death".

Kevorkian was born in Pontiac, Michigan. He graduated in medicine, in 1952, from the University of Michigan, Ann Arbor, and served two years as a medical officer in the U.S. Army. His postgraduate work has consisted of a residency in pathology (which he was completing while his book was at press) and medical research in Germany.

The brief volume is cast in the unusual form of "dialogue", which facilitates sharp contrast of viewpoints on various phases of the issue with which it is concerned. It also tends to involve the reader deeply in the dialectic. No argument is advanced regarding capital punishment *per se*—on the levels of either morality or effectiveness. The position rigidly adhered to is that, where the extreme penalty is invoked, society would benefit by utilizing the situation to advance knowledge.

This reviewer found the case presented a compelling one. He could not, however, avoid speculation that wide familiarity with the idea might induce grave doubts about the whole concept of capital punishment.

ALCOHOLISM: An Interdisciplinary Approach. Edited by D. J. Pittman. 95 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $4.00.

This book consists of the proceedings of the First Annual Conference on Community Mental Health held at the Social Science Institute, Washington University, St. Louis, Missouri, in 1959. Presumably, it reflects in some measure the importance of the problem of alcoholism and emphasizes that this subject should be the first of what may well be a series of conferences to be held at Washington University on various community health problems. Certainly, one can only commend such an effort.

However, the average reader will be forgiven if he approaches the published proceedings of such conferences with a certain amount of hesitancy. By and large, such proceedings represent a useful record for those who have attended the conference and possibly for those who might be planning a similar type of conference in the future. As a symposium on a particular subject there is often much to be desired. The contributors have usually stated their views more precisely and effectively in other publications.

In these respects, the present volume does not distinguish itself particularly from other such compilations. The presentations at the conference were made by competent and, in many cases, outstanding authorities in particular aspects of alcoholism. They present their views here with equal competence and authority but not with any degree of originality. Despite the sub-title "An Interdisciplinary Approach", there is very little material that truly interrelates the various points of view. Rather, we have a series of essays representing a variety of disciplines and their frequently isolated approaches to the problem.

The book may serve as a brief introduction to those who are not otherwise familiar with the many complexities of the alcoholism problem. Beyond this, it adds little, if anything, to the mass of material already available on the subject.

HELP BRINGERS: VERSATILE PHYSICIANS OF NEW JERSEY. Fred B. Rogers, Temple University School of Medicine, Philadelphia. 125 pp. Illust. Vantage Press, Inc., New York, 1960. $2.95.

We have too few records, such as this, of noteworthy but, alas, unnoted medical men. Dr. Rogers' 12 "help-bringers" are selected from the membership of the Medical Society of New Jersey, which dates back to 1766. There are no giants among them, as one thinks of giants in medicine, but we do not need to be looking up always to giants only; after all, they stand, or have mounted on the shoulders of others, some of whom have not themselves succeeded more because of circumstances than from the lack of great qualities. These are just the solid, honest, independent-minded men who have not only laid its foundation but in some way or other have added ornamentation and distinction to the medical social structure.

In the early pioneering days some of these men came through what is sometimes referred to in terms of "great tribulation". But perhaps too much stress should not be laid on their physical hardships—there were compensations of leisure and freedom from stress which we would welcome. Perhaps the place of such men is best described in the reference made to Dr. (Rev.) Robert McLean, the founder and first president of the Medical Society of New Jersey, by a presidential successor, Dr. Eagleton, speaking in 1923. "It is not," he said, "because Dr. McLean was a preacher, or even because he was a physician, that the physicians of today wish to perpetuate his memory; it is because of the standards which he and his associates set for those who have followed. . . ." This was the period when the physician could "with an easy span" take care of souls as well as of bodies, teaching, and affairs of state. The examples in this collection of sketches well illustrate this great variety of interests.

STUDIES ON VERTEBRATE NEUROGENESIS. S. Ramon y Cajal. Translated by Lloyd Guth, National Institutes of Health, Bethesda, Md. 432 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $14.75.

This collection of studies was selected by Cajal and was published in French translation in Madrid in 1929. English neurology owes a debt of gratitude to Dr. Guth for presenting these master works to us for the first time in our language.

The studies range widely and comprehensively over the whole field of neuro-embryology from general histogenesis, where Cajal reveals himself as a stout proponent of the "neuron doctrine", to the development of the complicated end-organs of the internal ear and the retina.

The book is fully illustrated by Cajal's original drawings, many of which are, of course, classics and have been used by teachers of neuro-anatomy for many years.

The translator has verified all of Cajal's references and he has added a useful author and subject index at the end of the book.

RADIATION: Use and Control in Industrial Application. C. W. Shilling, Deputy Director, Division of Biology and Medicine, United States Atomic Energy Commission, Washington, D.C. 223 pp. Illust. Grune & Stratton, Inc., New York, 1960. $6.75.

This excellent little monograph, though addressed primarily to those in the realm of industrial medicine, will undoubtedly interest a far larger audience. The author is the Deputy Director of the Division of Biology and Medicine of the United States Atomic Energy Commission, and from the tremendous volume of material obtained through this and other sources he has distilled an interesting and readable concentrate which will be welcomed by the general medical reader. There is a concise description of the natural sources of radiation as well as those of human origin, and their importance to mankind is presented in reasonable perspective. The subjects discussed include somatic and genetic effects of radiation, the handling of radiation accidents, the control of radiation, the prevention and treatment of radiation injury, and other related topics. For the increasing number of industrial physicians who are encountering radiation problems for the first time, it will be invaluable to have so brief and readable a discussion of subjects which are not readily abstracted from the voluminous literature. The material on radiobiology and protection contains information of particular value to student radiologists and x-ray technicians.

DIE ASBESTOSE DER LUNGEN. GENESE, KLINIK, ROENTGENOLOGIE. H. Bohlig, G. Jacob, and H. Müller. 166 pp. Illust. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1960. DM 59.40; $15.70.

For anyone who can read German fluently or who can struggle through it with the aid of a German-English dictionary, this volume is an excellent compendium of the knowledge of pulmonary asbestosis. The authors have gone deeply into the literature and cite with great frequency the findings of others. The bibliography is comprehensive.

The authors stress their dependence on accurate history and radiological findings for diagnosis. Asbestos bodies in the sputum are diagnostic, but unreliable because of the absence of sputum in many cases or because of the absence of such bodies even when sputum is copious. The fact that many different industries and occupations now employ asbestos is emphasized, so that the occupational history must be detailed and accurate in order to uncover cases of asbestosis when radiological findings are suggestive.

The radiographic reproductions are excellent, but one is left with the feeling that they are not diagnostic and that similar findings may occur in other diseases. The authors admit this, but still devote the major part of the book to radiographic findings. Considerable space is given to the symptomalogy and to clinical and laboratory findings none of which seem to be specific. One would have wished for more detailed pulmonary function studies than vital capacities, chest expansion and breath holding. Possibly these were unavailable at the time the studies were made.

The book is well set up in clear type, but the length of the lines sometimes makes for difficult reading.

The wealth of information on pulmonary asbestosis in this book would make it a valuable addition to any library on chest and industrial diseases.

FORTHCOMING MEETINGS

THE CANADIAN MEDICAL ASSOCIATION, 94th Annual Meeting, Montreal, Que., June 19-23, 1961. Dr. A. D. Kelly, General Secretary, 150 St. George St., Toronto 5, Ont.

CANADA

October

ONTARIO PUBLIC HEALTH ASSOCIATION, Toronto, Ont., October 3-5. Dr. G. K. Martin, Secretary-Treasurer, Room 405, 67 College St., Toronto, Ont.

THE CANADIAN MEDICAL ASSOCIATION, BRITISH COLUMBIA DIVISION, Annual Meeting, Vancouver, B.C., October 4-7. Dr. G. Gordon Ferguson, Executive Director, 1807 West 10th Ave., Vancouver 9, B.C.

COLLEGE OF PHYSICIANS AND SURGEONS OF SASKATCHEWAN—THE CANADIAN MEDICAL ASSOCIATION, SASKATCHEWAN DIVISION, Annual Meeting, Regina, Sask., October 18-21. Dr. G. W. Peacock, Secretary, 932 Spadina Crescent E., Saskatoon, Sask.

CANADIAN SOCIETY FOR THE STUDY OF FERTILITY, Toronto, Ont., October 21 and 22. Dr. George H. Arronet, Secretary, Infertility Centre, Royal Victoria Hospital, Montreal, Que.

November/December

CANADIAN HEART ASSOCIATION AND NATIONAL HEART FOUNDATION OF CANADA, Toronto, Ont., November 30-December 3. Dr. John B. Armstrong, National Heart Foundation, 501 Yonge St., Toronto 5, Ont.

1961

THE CANADIAN ASSOCIATION OF RADIOLOGISTS, Annual Meeting, Saint John, N.B., January 22-25, 1961. Dr. R. G. Fraser, Hon. Secretary-Treasurer, Ste. 204, 1555 Summerhill Ave., Montreal 25, Que.

COLLEGE OF GENERAL PRACTICE (MEDICINE) OF CANADA, Annual Meeting, Vancouver, B.C., March 20-23, 1961. Dr. W. V. Johnston, Executive Director, 150-A St. George St., Toronto 5, Ont.

UNITED STATES

September

AMERICAN SOCIETY OF CLINICAL PATHOLOGISTS, Chicago, Ill. September 24-October 2. Mr. Claude E. Wells, Executive Secretary, 445 Lake Shore Drive, Chicago 11, Ill.

October

AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC., New York, N.Y., October 2-7. Mr. John W. Andes, Executive Secretary, 188 West Randolph St., Chicago 1, Ill.

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AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA, Coronado, Cal., October 5-7. Dr. William T. Fitts Jr., Secretary, 300 Spruce St., Philadelphia 4, Penn.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY, CHICAGO, Ill., October 9-14. Dr. William L. Benedict, Executive Secretary, 15 Second St. S.W., Rochester, Minn.

CONGRESS ON INDUSTRIAL HEALTH, Charlotte, N.C., October 10-12. For information write—Council on Occupational Health, American Medical Association, 535 N. Dearborn St., Chicago 10, Ill.

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AMERICAN COLLEGE OF GASTROENTEROLOGY, Philadelphia, Pa., October 23-26. Mr. Daniel Weiss, Executive Director, 33 West 60th St., New York 23, N.Y.

AMERICAN PUBLIC HEALTH ASSOCIATION, San Francisco, Cal., October 30-November 4. Dr. Berwyn F. Mattison, Executive Director, 1790 Broadway, New York 19, N.Y.

November

AMERICAN SOCIETY OF TROPICAL MEDICINE AND HYGIENE, Los Angeles, Cal., November 2-5. Dr. Rolla B. Hill, Executive Secretary, 3572 St. Gaudens Rd., Miami 33, Fla.

ASSOCIATION OF CLINICAL SCIENTISTS (Applied Seminar on Measurements of Pancreatic Function in Clinical Medicine), Washington, D.C., November 4-5. Dr. F. William Sunderman, 1025 Walnut St., Philadelphia 7, Pa.

INTERNATIONAL SYMPOSIUM ON THE ETIOLOGY OF MYOCARDIAL INFARCTION, Henry Ford Hospital, Detroit, November 16-18. Dr. Thomas N. James, Henry Ford Hospital, Detroit 2, Chairman, Section of Cardiovascular Research.

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CONFERENCE ON GRADUATE MEDICAL EDUCATION—"Educational Problems in the Internship and Residency", Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pa., December 1-2. Dr. Paul Nemir Jr., Dean, 237 Medical Laboratories Bldg., Philadelphia 4, Pa.

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY, Chicago, Ill., December 3-8. Dr. Robert R. Kierland, Secretary-Treasurer, First National Bank Bldg., Rochester, Minn.

RADIOLOGICAL SOCIETY OF NORTH AMERICA, Cincinnati, Ohio, December 4-9. Dr. Donald S. Childs, Secretary, 713 E. Genesee St., Syracuse 2, N.Y.

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AMERICAN ACADEMY OF OCCUPATIONAL MEDICINE, Detroit, Mich., February 8-10, 1961. Dr. Paul J. Whitaker, Secretary, Allis Chalmers Mfg. Co., P.O. Box 512, Milwaukee 1, Wis.

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NEUROSURGICAL SOCIETY OF AMERICA (members and guests), Boca Raton, Fla., March 8-11, 1961. Dr. Raymond K. Thompson, Secretary, 803 Cathedral St., Baltimore 1, Md.

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AMERICAN ASSOCIATION OF ANATOMISTS, Chicago, Ill., March 28-31, 1961. Dr. Louis B. Flexner, Secretary-Treasurer, Department of Anatomy, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa.

OTHER COUNTRIES

September/October

PAN PACIFIC SURGICAL ASSOCIATION, Eighth Congress, Honolulu, Hawaii, September 28-October 5. Dr. F. J. Pinkerton, Director General, Suite 230, Alexander Young Bldg., Honolulu 13, Hawaii.

October

SYMPOSIUM ON DIAGNOSIS AND TREATMENT OF ACUTE RADIATION SICKNESS, Geneva, Switzerland, October 17-22. World Health Organization, Palais des Nations, Geneva, Switzerland.

PAN AMERICAN CONGRESS OF GASTROENTEROLOGY, Santiago, Chile, October 23-29. Dr. Ricardo Katz, Secretary General, c/o Servicio de Medicina, Hospital del Salvador, Casilla 70-D, Santiago, Chile.

November

MEDICAL SOCIETY OF THE UNITED STATES AND MEXICO, Fifth Annual Meeting, Guadalajara, Jal., Mexico, November 8-10, followed by Mazatlan, Sin., Mexico, November 11-12, Dr. M. A. Carreras, 130 South Scott, Tucson, Arizona.

BAHAMAS MEDICAL CONFERENCE, British Colonial Hotel, Nassau, November 25-December 16. Mr. Irvin M. Wechsler, P.O. Box 1454, Nassau, Bahamas, General Manager.

LATIN AMERICAN CONGRESS OF NEUROLOGY, Santiago, Chile, November 27-December 1, Prof. Rodolfo Nunez, Almirante Montt 485, Dep. 11, Santiago, Chile.

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1961

AMERICAN COLLEGE OF SURGEONS, SECTIONAL MEETING, Hotels Del Prado, Reforma, Vista Hermosa, El Presidente, Alffer, Continental Hilton, Mexico City, January 23-26, 1961. Dr. William E. Adams, 40 E. Erie Street, Chicago 11, Ill., Secretary.

Canad. M. A. J.
Sept. 24, 1960, vol. 83

RADIATION: Use and Control in Industrial Application. C. W. Shilling, Deputy Director, Division of Biology and Medicine, United States Atomic Energy Commission, Washington, D.C. 223 pp. Illust. Grune & Stratton, Inc., New York, 1960. $6.75.

This excellent little monograph, though addressed primarily to those in the realm of industrial medicine, will undoubtedly interest a far larger audience. The author is the Deputy Director of the Division of Biology and Medicine of the United States Atomic Energy Commission, and from the tremendous volume of material obtained through this and other sources he has distilled an interesting and readable concentrate which will be welcomed by the general medical reader. There is a concise description of the natural sources of radiation as well as those of human origin, and their importance to mankind is presented in reasonable perspective. The subjects discussed include somatic and genetic effects of radiation, the handling of radiation accidents, the control of radiation, the prevention and treatment of radiation injury, and other related topics. For the increasing number of industrial physicians who are encountering radiation problems for the first time, it will be invaluable to have so brief and readable a discussion of subjects which are not readily abstracted from the voluminous literature. The material on radiobiology and protection contains information of particular value to student radiologists and x-ray technicians.

DIE ASBESTOSE DER LUNGEN. GENESE, KLINIK, ROENTGENOLOGIE. H. Bohlig, G. Jacob, and H. Müller. 166 pp. Illust. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1960. DM 59.40; $15.70.

For anyone who can read German fluently or who can struggle through it with the aid of a German-English dictionary, this volume is an excellent compendium of the knowledge of pulmonary asbestosis. The authors have gone deeply into the literature and cite with great frequency the findings of others. The bibliography is comprehensive.

The authors stress their dependence on accurate history and radiological findings for diagnosis. Asbestos bodies in the sputum are diagnostic, but unreliable because of the absence of sputum in many cases or because of the absence of such bodies even when sputum is copious. The fact that many different industries and occupations now employ asbestos is emphasized, so that the occupational history must be detailed and accurate in order to uncover cases of asbestosis when radiological findings are suggestive.

The radiographic reproductions are excellent, but one is left with the feeling that they are not diagnostic and that similar findings may occur in other diseases. The authors admit this, but still devote the major part of the book to radiographic findings. Considerable space is given to the symptomalogy and to clinical and laboratory findings none of which seem to be specific. One would have wished for more detailed pulmonary function studies than vital capacities, chest expansion and breath holding. Possibly these were unavailable at the time the studies were made.

The book is well set up in clear type, but the length of the lines sometimes makes for difficult reading.

The wealth of information on pulmonary asbestosis in this book would make it a valuable addition to any library on chest and industrial diseases.

FORTHCOMING MEETINGS

THE CANADIAN MEDICAL ASSOCIATION, 94th Annual Meeting, Montreal, Que., June 19-23, 1961. Dr. A. D. Kelly, General Secretary, 150 St. George St., Toronto 5, Ont.

CANADA

October

ONTARIO PUBLIC HEALTH ASSOCIATION, Toronto, Ont., October 3-5. Dr. G. K. Martin, Secretary-Treasurer, Room 405, 67 College St., Toronto, Ont.

THE CANADIAN MEDICAL ASSOCIATION, BRITISH COLUMBIA DIVISION, Annual Meeting, Vancouver, B.C., October 4-7. Dr. G. Gordon Ferguson, Executive Director, 1807 West 10th Ave., Vancouver 9, B.C.

COLLEGE OF PHYSICIANS AND SURGEONS OF SASKATCHEWAN—THE CANADIAN MEDICAL ASSOCIATION, SASKATCHEWAN DIVISION, Annual Meeting, Regina, Sask., October 18-21. Dr. G. W. Peacock, Secretary, 932 Spadina Crescent E., Saskatoon, Sask.

CANADIAN SOCIETY FOR THE STUDY OF FERTILITY, Toronto, Ont., October 21 and 22. Dr. George H. Arronet, Secretary, Infertility Centre, Royal Victoria Hospital, Montreal, Que.

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1961

AMERICAN COLLEGE OF SURGEONS, SECTIONAL MEETING, Hotels Del Prado, Reforma, Vista Hermosa, El Presidente, Alffer, Continental Hilton, Mexico City, January 23-26, 1961. Dr. William E. Adams, 40 E. Erie Street, Chicago 11, Ill., Secretary.

Books Received

Books are acknowledged as received, but in some cases reviews will also be made in later issues.

Oral Pathology. K. H. Thoma, Professor of Oral Surgery, Boston University School of Medicine, Boston, and H. M. Goldman, Professor of Stomatology and Chairman of the Department, Boston University School of Medicine, Boston. 1523 pp. Illust. 5th ed. The C. V. Mosby Co., St. Louis, 1960. $27.50.

Nonpenetrating Injuries of the Abdomen. R. H. Kennedy, Consulting Surgeon, Beekman-Downtown, Bellevue and University Hospitals, New York. Edited by L. R. Dragstedt. 121 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $5.25.

Nonnarcotic Drugs for the Relief of Pain and Their Mechanism of Action. Annals of the New York Academy of Sciences. F. M. Berger (Conference Chairman). Vol. 86, Art. 1. The New York Academy of Sciences, New York, 1960. $3.50.

Molecular Organization in Solid High Polymers. Annals of the New York Academy of Sciences. F. R. Eirich (Conference Chairman). Vol. 83, Art. 1. 76 pp. Illust. The New York Academy of Sciences, New York, 1959. $3.00.

Memoirs of the Institute for Protein Research, Osaka University. Toshizo Isemura. Vol. 2. 287 pp. Illust. Institute for Protein Research, Osaka University, Osaka, Japan, 1960.

Mental Subnormality. W. A. Heaton-Ward, Medical Superintendent, Stoke Park Hospital Group, Bristol. 64 pp. Illust. John Wright & Sons Ltd., Bristol; The Macmillan Company of Canada Limited, Toronto, 1960. $1.00.

Les globulines sériques du système Gamma: Leur nature et leur pathologie. J. Heremans. 340 pp. Illust. Editions Arscia s.a., Bruxelles, 1960.

Internal Medicine: A Physiologic and Clinical Approach to Disease. R. P. McCombs, Professor of Graduate Medicine, Tufts University School of Medicine. 750 pp. Illust. 2nd ed. Year Book Publishers, Inc., Chicago, 1960. $10.50.

Inactivation of Viruses. Annals of the New York Academy of Sciences. E. C. Pollard and A. R. Taylor (Conference Co-Chairmen). Vol. 83, Art. 4. 513-760 pp. Illust. The New York Academy of Sciences, New York, 1960. $4.00.

Help Bringers: Versatile Physicians of New Jersey. Fred B. Rogers, Temple University School of Medicine, Philadelphia. 125 pp. Illust. Vantage Press, Inc., New York, 1960. $2.95.

MEDICAL NEWS *in Brief*

(Continued from page 725)

CANCER RESEARCH FELLOWSHIPS

The National Cancer Institute of Canada offers a number of Research Fellowships. They are designed to provide advanced training and experience in cancer research for individuals who plan a career in which furthering knowledge about cancer will be a major interest. These Fellowships are not awarded for the purpose of providing practical clinical training (Clinical Fellowships are provided by the Canadian Cancer Society).

Fellowships are open on equal terms to men and women and are awarded to the applicants who are deemed best qualified on the evidence submitted. A candidate must be a graduate of a university approved by the Institute. Research Fellowships are normally tenable in Canada.

The value of Fellowships will depend on the training and experience of the candidate. Tenure and payment of a Fellowship shall normally commence on April 1 or July 1.

Application for a Fellowship must be made by the candidate to the National Cancer Institute of Canada on an official form on or before December 15 of the preceding year.

A copy of the regulations concerning these Fellowships together with application forms may be obtained from the National Cancer Institute of Canada, 790 Bay Street, Toronto, Ont.

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UROLOGY AWARD

The American Urological Association offers an annual award of $1000 (first prize of $500, second prize $300, and third prize $200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been graduated not more than ten years, and to hospital interns and residents doing research work in urology.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Biltmore, Los Angeles, California, May 22-25, 1961.

For full particulars write to the Executive Secretary, William P. Didusch, 1120 North Charles Street, Baltimore, Maryland. Essays must be in his hands before December 1, 1960.

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CATHOLIC HOSPITAL ASSOCIATION PUBLICATION ON CARE OF THE AGED

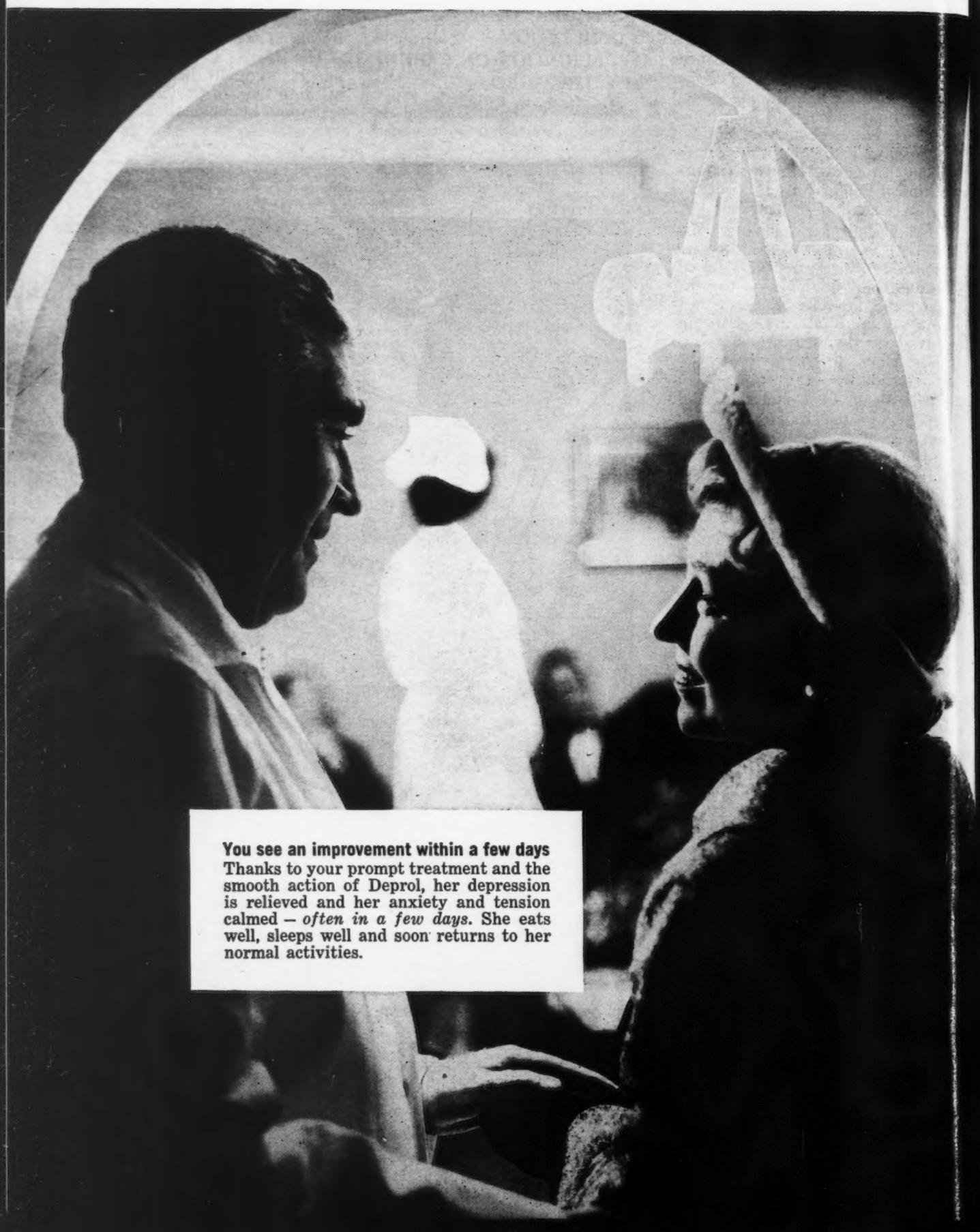
The new Catholic Hospital Association publication on the care of the aged, "The Administration of Long-Term Care Facilities," is now available.

Sixteen recognized authorities in the field of geriatric care present material relating to the various aspects of care for the aged in an institutional setting. The papers also deal with problems of administration in such facilities.

The book is a collection of papers originally presented at an institute held in St. Cloud, Minn., sponsored by the Catholic Hospital

(Continued on page 26)

Lifts depression...



You see an improvement within a few days
Thanks to your prompt treatment and the smooth action of Deprol, her depression is relieved and her anxiety and tension calmed – *often in a few days.* She eats well, sleeps well and soon returns to her normal activities.

as it calms anxiety!

Smooth, balanced action lifts depression as it calms anxiety... rapidly and safely

Balances the mood – no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient *–they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation–*they often deepen depression.*

In contrast to such "seesaw" effects, Deprol's smooth, *balanced* action lifts depression as it calms anxiety–both at the same time.

Acts swiftly – the patient often feels better, sleeps better, within a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

Acts safely – no danger of liver damage. Deprol does not produce liver damage, hypotension, psychotic reactions or changes in sexual function–frequently reported with other antidepressant drugs.

Bibliography *(13 clinical studies, 858 patients):* **1.** Alexander, L. (35 patients): Chemotherapy of depression – Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. **2.** Bateman, J. C. and Carlton, H. N. (50 patients): Meprobamate and benactyzine hydrochloride (Deprol) as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy 6:648, Nov. 1959. **3.** Beerman, H. M. (44 patients): The treatment of depression with meprobamate and benactyzine hydrochloride. Western Med. 1:10, March 1960. **4.** Bell, J. L., Tauber, H., Santy, A. and Pulito, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. **5.** Breitner, C. (31 patients): On mental depressions. Dis. Nerv. System 20:142, (Section Two), May 1959. **6.** Gordon, P. E. (50 patients): Deprol in the treatment of depression. Dis. Nerv. System 21:215, April 1960. **7.** Landman, M. E. (50 patients): Clinical trial of a new antidepressive agent. J. M. Soc. New Jersey. In press, 1960. **8.** McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression – New technics and therapy. Am. Pract. & Digest Treat. 10:1525, Sept. 1959. **9.** Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. **10.** Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. **11.** Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. **12.** Settel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy 7:28, Jan. 1960. **13.** Splitter, S. R. (84 patients): Treatment of the anxious patient in general practice. J. Clin. & Exper. Psychopath. In press, April-June 1960.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

Deprol†

† TRADE-MARK

WALLACE LABORATORIES / *Toronto, Ontario*

MEDICAL NEWS *in brief*

(Continued from page 23)

Association of the United States and Canada and the Diocese of St. Cloud, which attracted attention of representatives from nursing homes in 15 states.

Price of the publication is $1.50 each. Quantity prices are available on request from the Publications Department, Catholic Hospital Association, 1438 South Grand Blvd., St. Louis 4, Mo.

FELLOWSHIP IN CARDIAC ROENTGENOLOGY

A Fellowship in Cardiac Roentgenology will be offered beginning January 1, 1961, by the Department of Medicine in co-operation with the Department of Radiology of Duke Medical Center to residents who have successfully completed at least two and preferably three years' training in radiology. For further details write Henry D. McIntosh, M.D., Associate Professor of Medicine, Duke Medical Center, Durham, N.C.

REFRESHER COURSE IN EYE SURGERY, UNIVERSITY OF TORONTO

The Faculty of Medicine, University of Toronto, will hold a Refresher Course in Eye Surgery March 20-22, 1961. The instruction will consist of lectures, operative sessions and a special symposium on cataract surgery.

Dr. Robert N. Shaffer, University of California, San Francisco, and Mr. B. W. Rycroft, F.R.C.S., London, England, will be guest surgeons. The staff of the Department of Ophthalmology will contribute extensively.

The course will be limited to 50 members and is open to eye, ear, nose and throat specialists. Application should be made to the Director, Division of Postgraduate Medical Education, Faculty of Medicine, University of Toronto, Toronto 5, Ontario, before January 31, 1961.

On March 18 there will be a Departmental Research meeting and Dr. H. M. Burian, University of Iowa, will be guest speaker. Members of the Eye Surgery Course are invited to attend.

SOCIETY FOR INDUSTRIAL MICROBIOLOGY

The Society for Industrial Microbiology will sponsor a Conference on Antimicrobial Agents at the Mayflower Hotel, Washington, D.C., October 26-28.

Some 500 scientists from the United States and abroad are expected to attend, and about 125 technical papers will be read. The Conference is designed to succeed annual antibiotics symposia conducted for the past seven years by Dr. Henry Welch. The new sponsors have no connection with the management of the previous symposia. The former sponsors will not conduct a symposium this year.

In announcing plans for the conference, Dr. Charles Yeager, Chicago, president of the Society for Industrial Microbiology, said:

"Developments in research activities in the important field of antimicrobial agents are so rapid that an annual gathering of scien-

tists is of great importance to the individual scientists and to research activity and progress.

"With proper control, a meeting at which scientists can exchange ideas and learn of new developments by others can be of great benefit.

"In making arrangements for the 1960 gathering, we are taking steps to guarantee that no abuses of privilege will creep in, and that no person, corporation or agency will benefit financially.

"Specifically, it will be required that all papers be submitted in advance and be screened by a well-qualified editorial committee. Any interested scientist will be free to submit abstracts and papers for the Conference.

"Reprints will be distributed only on a carefully controlled basis by the SIM Publications Committee.

"The proceedings of the Conference will be published under arrangements controlled by the SIM Publications Committee.

"With these measures, we believe that a successful, creative, and constructive result can be achieved which will benefit all biological science."

Program sections for the Conference will include sessions on "The Mode of Antibiotic Action", "New Anti-fungal Compounds", "Anti-tumour and Anti-virus Compounds", "Clinical Response to Antibiotics", "Isolation and Production of New Antibiotics and Synthetic Production of Natural Antibiotics", "Laboratory Problems of Sensitivity and Resistance of Pathogenic Organisms" and "Chemotherapeutic Substances and Compounds".

Dr. Lloyd G. Herman, president-elect of the Washington, D.C., section of the Society for Industrial Microbiology, is chairman of arrangements for the Conference. The Conference address is: c/o Society for Industrial Microbiology, 2000 P Street, N.W., Washington 6, D.C. Also on the arrangements committee is Dr. Walter Bejuki, president of the Washington section of SIM. Subcommittees of scientists are being formed to handle details.

The Society for Industrial Microbiology is an organization of scientists employed by colleges and universities, government and public health agencies, and by firms in the food, textile, pharmaceutical, chemical, petroleum and electronics industries.

AMERICAN HEART ASSOCIATION ISSUES NEW REPORT ON CIGARETTE SMOKING AND HEART DISEASE

A report by Dr. A. Carlton Ernstene, President of the American Heart Association, cites a number of recent medical studies showing a statistical association between heavy cigarette smoking and mortality or morbidity from coronary heart disease. In nearly all of these studies, the death rate from coronary disease in middle-aged men was found to be from 50 to 150% higher among heavy cigarette smokers than among those who did not smoke. This does not prove that heavy cigarette smoking causes coronary disease, but the data strongly suggest that heavy cigarette smoking may contribute to or accelerate the development

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of this form of heart disease or its complications.

"Because coronary heart disease is the leading cause of death and the major cause of disability in the American population, the American Heart Association believes that these studies concerning cigarette smoking and coronary heart disease should be called to the attention of the medical profession, allied health professions, health educators, and the general public. The Association recognizes the need for more knowledge and will continue to encourage systematic biological and medical research in order to determine whether a causal relationship exists between cigarette smoking and coronary heart disease and also to determine the effect of smoking in relation to strokes and other important aspects of cardiovascular disease."—Ad Hoc Committee on Smoking and Cardiovascular Disease: L. N. Katz, M.D., Chairman, E. V. Allen, M.D., M. Cherkasky, M.D., F. W. Davies, M.D., T. R. Dauber, M.D.

WEEKLY MEDICAL NEWS REVIEW ON OPEN TELEVISION

A weekly review of medical news for physicians, using regular commercial television channels, will go on the air October 30 over a nationwide network in the United States.

The 15-minute program, "This Week in Medicine," will be broadcast on Sunday afternoons. The selection of the broadcast time was based on preference expressed by physicians in cities where the program was tested with the co-operation of county medical societies.

Tests in four cities—Dallas, Kansas City, Miami and Binghamton—showed that even though "This Week in Medicine" could be seen by the public over regular channels, the technical language and subject matter limited the audience to physicians and members of allied health professions.

Using video tape and film, each program will include a world-wide summary of medical news and a filmed feature on some aspect of research, clinical medicine or surgery. It will mark the first use of regular television channels to reach a nationwide medical audience on a professional level.

PICKER FOUNDATION AWARDS IN CANADA

Dr. J. S. Dunbar, of the Montreal Children's Hospital, has been awarded a grant of $4500 by the James Picker Foundation of the United States. The award is to assist Dr. Dunbar in radiological research — specifically, to study factors affecting the "concentration of opaque medium in intravenous pyelography".

A Picker award has also been made to Dr. Guido Castorina of Rome, Italy, who will undertake neuroradiological studies of congenital and acquired epilepsies at the Montreal Neurological Institute. This work will be under the direction of Dr. Donald L. McRae.

These announcements were made recently by the National Research Council of Canada, which administers the Canadian program of the James Picker Foundation. The American program, which this year made awards totalling $121,000, is administered by the

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MEDICAL NEWS *in brief*

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National Academy of Sciences, National Research Council, Washington, D.C.

POSTGRADUATE COURSES ON DISEASES OF THE CHEST

Two postgraduate courses on diseases of the chest have been announced by Dr. J. Winthrop Peabody, Sr., Washington, D.C., Chairman of the Council on Postgraduate Medical Education of the American College of Chest Physicians.

The first of these, the 15th annual course, Clinical Cardiopulmonary Physiology, has been arranged under the co-chairmanship of Dr. Albert H. Andrews, Associate Clinical Professor of Bronchoesophagology, University of Illinois College of Medicine, and Dr. Edwin R. Levine, Assistant Professor of Clinical Medicine, Chicago Medical School. This course will be held at the Sheraton Towers Hotel, Chicago, October 24-28, 1960.

The second, the 12th annual course, Recent Advances in the Diagnosis and Treatment of Diseases of the Heart and Lungs, was arranged under the co-chairmanship of Dr. Edgar Mayer, Clinical Professor of Medicine, New York University Postgraduate Medical Center; Dr. Alfred S. Dooneief, Lecturer in Medicine, Columbia University College of Physicians and Surgeons; and Dr. Emil A. Naclerio, Chief, Thoracic Surgical Services, Harlem and Columbus Hospitals, New York City. This course will take place at the Park Sheraton Hotel, New York City, November 14-18, 1960.

Tuition for each five-day course will be $100 including round table luncheon discussions.

For additional information, write to: Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Ill.

POSTGRADUATE COURSE IN ALLERGY

A continuous course of two weeks' duration is being offered by the Departments of Allergy and Applied Immunology of the Temple University Medical Center and the Graduate School of Medicine of the University of Pennsylvania. Sessions will be held daily at the Temple University Medical Center from 9:00 a.m. to 5:00 p.m. from February 27 to March 10, 1961. The tuition fee is $175.00 and enrolment is limited.

The course will be devoted to a review of the basic principles of immunology and allergy as applied to clinical practice. Emphasis will be given to the methods of diagnosis and management of the allergic patient.

The course is designed for physicians desirous of extending their knowledge of allergy. It could serve as an introductory course for those about to enter the field or as a review course for practising allergists.

For brochure and application forms write to: Dr. George Blumstein, c/o Temple Medical Center, Philadelphia 40, Pa.

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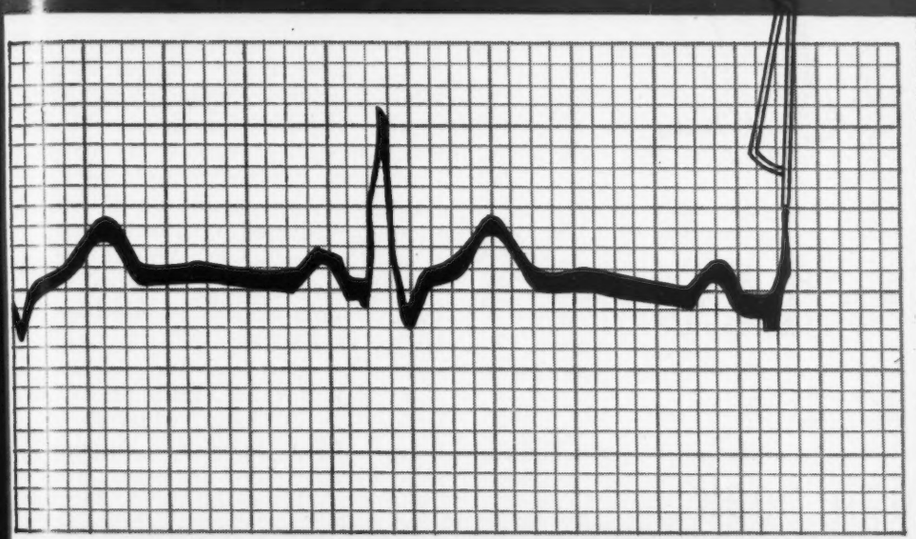

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***In Coronary Thrombosis death rate reduced one-third thromboembolic complications one-half**

Manchester[3] has reported on 550 patients followed for up to 10 years. In the control group there were two to three times more subsequent myocardial infarction and various thromboembolic episodes than in the anticoagulant treated group. Mortality from subsequent infarction or thromboembolism was about 20 per cent in the treated and about 50 per cent in the control group.

In a study[4] of 1031 cases by the Committee on Anticoagulants of the American Heart Association the mortality rate in myocardial infarction was 16 per cent in the anticoagulant group compared with 23.4 per cent in the control group. Incidence of thromboembolic complications was 13.1 per cent in the anticoagulant group compared with 41.8 per cent in the control group.

Comprehensive bibliography and literature available on request.

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1. Lange, K; Perchuk, E. and Mahl, M. M.: American Heart Journal, 55:1, 1958.
2. Blaustein, A.: N.Y. St. J. Med., 58:5, 1958.
3. Manchester, B: The prevention of subsequent myocardial infarction. A.M.A. Meeting, New York, June, 1957.
4. Wright, I. S., Marple, C. D. and Beck, D. F.: Myocardial Infarction, Its Clinical Manifestations and Treatment with Anticoagulants. New York, Grune & Stratton, 1954.

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THE AMERICAN COLLEGE OF PHYSICIANS' SCHEDULE OF POSTGRADUATE COURSES, AUTUMN-WINTER, 1960-61

Cancer and the Internist—1960 Concepts: Memorial Center, Sloan-Kettering Institute for Cancer Research, New York, N.Y.; Rulon W. Rawson, M.D., F.A.C.P., Director. October 10-14.

The Physiologic Basis of Electrocardiography: University of Utah College of Medicine, Salt Lake City, Utah; Hans H. Hecht, M.D., F.A.C.P., Director. November 7-11.

Recent Advances in Drug Therapy: University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director. January 9-13, 1961.

Mechanisms of Disease: Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York, N.Y.; Alfred P. Fishman, M.D., F.A.C.P., and Stanley E. Bradley, M.D., F.A.C.P., Co-Directors. January 16-20, 1961.

Selected Topics in Internal Medicine: The University of Oklahoma School of Medicine and University Hospitals, Oklahoma City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., and James F. Hammarsten, M.D., F.A.C.P., Co-Directors; William O. Smith, M.D. (Associate), Associate Director. February 20-24.

The following courses are also scheduled for 1961: Cardiovascular Diseases, Mount Sinai Hospital, Charles K. Friedberg, M.D., F.A.C.P., Director, March 6-10; Internal Medicine, McGill University, Ronald V. Christie, M.D., F.A.C.P., Director, March 13-17; Advanced Clinical Electrocardiography, The University of Tennessee, I. Frank Tullis, M.D., F.A.C.P., Director, March 20-24; Endocrinology, University of Virginia, William Parson, M.D., F.A.C.P., Director, March 23-25; Problems of Growth and Ageing, Lankenau Medical Building, Philadelphia, Edward L. Bortz, M.D., F.A.C.P., Director, April 12-15; Gastroenterology, University of Pennsylvania School of Medicine; Henry L. Bockus, M.D., F.A.C.P., Director, May 15-19; Current Aspects of Internal Medicine, State University of Iowa, William B. Bean, M.D., F.A.C.P., Director, June 19-23.

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SYMPOSIUM ON SURGERY OF ENDOCRINE ORGANS

A three-day symposium, Surgery of Endocrine Organs, will be presented by the schools of medicine of the New York University Medical Center, from November 17 to 19, 1960.

Surgical diseases in which the endocrine system is directly involved or in which endocrine influences are important will be discussed. Functioning tumours of endocrine structures, derangements of internal secretions that are amenable to surgical treatment, and endocrine factors in metastases of cancer will be considered from physiological and diagnostic standpoints.

A round table discussion by all the participants on Saturday morning, November 19, will conclude the symposium.

Further details may be obtained from the Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16, N.Y.